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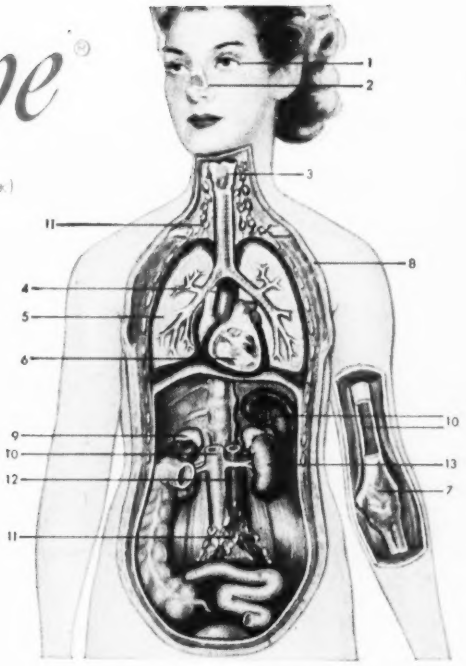


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1. Bargen: Chronic Ulcerative Colitis. Charles C Thomas, Publisher. 1951. Springfield, Illinois.

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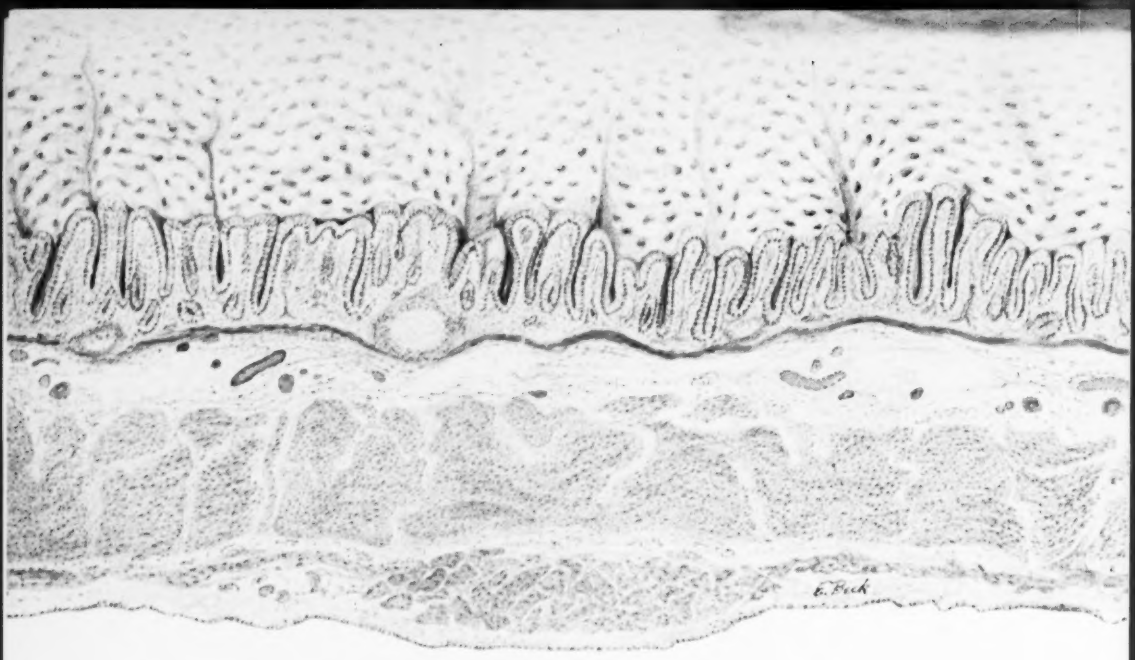

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ARCHIVES OF INTERNAL MEDICINE

VOLUME 91 JANUARY 1953 NUMBER 1

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# ADRENOCORTICAL FUNCTION DURING CONTINUOUS LONG-TERM THERAPY WITH CORTISONE

EPHRAIM P. ENGLEMAN, M.D.
MARCUS A. KRUPP, M.D.
HAROLD P. JOHNSON Jr., M.D.
JOSEPH E. WELSH, M.D.
HAROLD T. WRENN, Ph.B.
AND
WILBERT R. KING
SAN FRANCISCO

SUPPRESSION of adrenocortical function and atrophy of the adrenal cortex have been described as following administration of cortisone.[1] Both effects, presumably, are due to suppression of secretion of corticotropin, with resulting inac-

Read before the meeting of the American Rheumatism Association, Chicago, June 6, 1952.

From the Medical Service, Veterans Administration Hospital, and the Division of Medicine, University of California School of Medicine, and Stanford University School of Medicine.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Ingle, D. J., and Kendall, E. C.: Atrophy of the Adrenal Cortex of the Rat Produced by the Administration of Large Amounts of Cortin, Science **86**:245, 1937. Ingle, D. J.: The Effects of Administering Large Amounts of Cortin on the Adrenal Cortices of Normal and Hypophysectomized Rats, Am. J. Physiol. **124**:369, 1938. Ingle, D. J., and Mason, H. L.: Subcutaneous Administration of Cortin Compounds in Solid Form to the Rat, Proc. Soc. Exper. Biol. & Med. **39**:154, 1938. Laquer, G. L.: Cytological Changes in Human Hypophyses After Cortisone and ACTH Treatment, Science **112**:429, 1950. Golden, A.; Bondy, P. K., and Sheldon, W. H.: Pituitary Basophile Hyperplasia and Crooke's Hyaline Changes in Man After ACTH Therapy, Proc. Soc. Exper. Biol. & Med. **74**:455, 1950. Sayers, G., and Sayers, M. A.: Pituitary-Adrenal System, Ann. New York Acad. Sc. **50**:522, 1949. Sprague, R. G.; Mason, H. L.; Mathiesen, D. R.; Bennett, W. A., and Gastineau, C. F.: Observations on the Effect of Cortisone on Adrenal Cortical Structure and Function in Man, in Proceedings of the Second Clinical ACTH Conference, Vol. II: Therapeutics, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, p. 38. Sprague, R. G., and others: Observations on the Physiologic Effects of Cortisone and ACTH in Man, Arch. Int. Med. **85**:199, 1950. Hench, P.: Effects of Cortisone in the Rheumatic Diseases, Lancet **2**:483, 1950. Forsham, P. H.; Thorn, G. W.; Frawley, T. F., and Wilson, L. W.: Studies on Functional State of the Adrenal Cortex During and Following ACTH and Cortisone Therapy, J. Clin. Invest. **29**:812, 1950. McIntosh, H. W., and Holmes, C. B.: Suppression of Adrenal Cortex Function by Cortisone, Lancet **2**:1061, 1951. Freyberg, R. H., and others: Problems of Prolonged Cortisone Treatment for Rheumatoid Arthritis, J. A. M. A. **147**:1538, 1951. Boland, E. W., and Headley, N. E.: Results of Long-Continued Cortisone Administration in Rheumatoid Arthritis, California Med. **74**:416, 1951. Sprague, R. G.: Cortisone and ACTH: A Review of Certain Physiologic Effects and Their Clinical Implications, Am. J. Med. **10**:567, 1951.

tivity of the adrenal cortex. Thus, the use of cortisone in interrupted courses, or of cortisone and exogenous corticotropin in alternating courses, has been recommended in order to produce periodic reactivation of the adrenal cortex. Obviously it is important to know whether the suppression of adrenocortical activity which results from long-term treatment with cortisone is reversible. A number of studies [1] have suggested that this is the case, but this conclusion usually has been based on observations of patients who had received large doses of cortisone for relatively short periods. Furthermore, the eosinopenia following administration of corticotropin was often the sole criterion of adrenocortical responsiveness.

TABLE 1.—*Data on Subjects Receiving Sixteen-Hour Intravenous Infusions of Twenty-Five Units of Corticotropin Daily*

| | Patients Treated with Cortisone* | | | | | | | | | | Controls Untreated with Cortisone or Corticotropin | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Name | Coo. | L. Lew. | Mac. | Yah. | Mah. | Sig. | Pos. | Med. | Hal. | Emi. | Lou. | Loe. |
| Age | 30 | 58 | 26 | 28 | 40 | 40 | 47 | 41 | 63 | 43 | 42 | 30 |
| Diagnosis† | R. A. | R. A. | R. A. | R. A. | R. A. | Der. | R. A. | Der. | R. A. | R. A. | Eales' Disease | Buerger's Disease |
| Daily dose of cortisone, mg.. | 62.5 | 100 | 62.5 | 75 | 75 | 75 | 100 | 37.5 | 50 | 62.5 | .. | .. |
| Duration of treatment with cortisone, mo. ..... | 15 | 24 | 12 | 14 | 22 | 16 | 17 | 15 | 26 | 20 | .. | .. |
| No. of successive days of corticotropin therapy required for adrenal response..... | 3 | 1 | 2 | 2 | 3 | 1 | 3 | 1 | 2 | 1 | 1 | 1 |
| Precorticotropin determinations: | | | | | | | | | | | | |
| Eosinophiles ..... | 337 | 153 | 180 | 141 | 156 | 213 | 0 | 114 | 132 | 272 | 150 | 96 |
| 24-hr. urinary ketosteroids, mg. ..... | 15.4 | 10.4 | 11.4 | 14.7 | 11.1 | 8.5 | 8.0 | 8.2 | 7.4 | 12 | 12 | 9.0 |
| 24-hr. urinary corticoids, mg. ..... | 0 | 0.5 | 0.31 | 0 | 0.38 | 0 | 0.28 | 0 | 0 | 0 | 0 | 0 |
| Determinations on day of adrenal response to corticotropin: | | | | | | | | | | | | |
| Eosinophiles ..... | 102 | 99 | 9 | 145 | 30 | 6 | 0 | 21 | .. | 121 | 0 | 3 |
| 24-hr. urinary ketosteroids, mg. ..... | 36.9 | 16.0 | 26.6 | 27.7 | 18.5 | 18.7 | 18.8 | 12.8 | 18.7 | 22.8 | 22.5 | 15.8 |
| 24-hr. urinary corticoids, mg. ..... | 0.47 | 1.1 | 1.3 | 1.37 | 1.1 | 1.4 | 1.4 | 0 | 1.7 | 0 | 1.9 | 0.8 |

* During test period daily doses of cortisone were continued.
† R. A. indicates rheumatoid arthritis, and Der. means dermatitis.

## MATERIAL AND METHOD

The purpose of this study was to assess critically the function of the adrenal cortex in 19 patients who were given so-called maintenance doses of cortisone for long periods. All patients had been treated with cortisone [2] continuously and without interruption for 12 to 26 months.

Five of these patients had been subjects of a similar study one year previously. The cortisone was administered orally and in daily doses ranging from 37.5 to 100 mg.; for one patient the daily dose was 150 mg. Hospital patients who had not received cortisone or corticotropin served as a control group. Details concerning the treated and the control groups of patients are given in Tables 1, 2 and 3.

The method of study consisted of the administration of corticotropin on successive days until two of the following three criteria of adrenal responsiveness were satisfied: (1) a 60% or greater decrease in circulating eosinophiles; (2) an increase of 50% or more in the 24-hour urinary excretion of 17-ketosteroids, and (3) an increase of 50% or more in the 24-hour urinary excretion of Porter-Silber chromogens (17, 21-hydroxy-20-ketosteroids), with a minimum

2. Cortisone was made available through the courtesy of Dr. Elmer Alpert, Manager of Clinical Research, Merck & Co., Inc., Rahway, N. J.

rise of 0.5 mg. The maintenance oral doses of cortisone were continued without interruption throughout the test period. Pilot's staining method[3] was used for counting the eosinophiles. When corticotropin was given in a continuous intravenous infusion over a 16-hour period,

TABLE 2.—*Data on Subjects Receiving Three-Hour Intravenous Infusions of 25 Units of Corticotropin for Two Successive Days, Followed by Daily Sixteen-Hour Intravenous Infusions of 25 Units*

| | Patients Treated with Cortisone* | | | | Controls Untreated with Cortisone or Corticotropin | | |
|---|---|---|---|---|---|---|---|
| Name | Low. | Sal. | B. Phl. | Kle. | Ska. | Bur. | Sch. |
| Age | 35 | 36 | 30 | 53 | 45 | 34 | 64 |
| Diagnosis† | R. A. | R. A. | R. A. | Asthma | Hiatus Hernia | Chronic Nephritis | R. A. |
| Daily dose of cortisone, mg. | 75 | 82.5 | 100 | 100 | ... | ... | ... |
| Duration of treatment with cortisone, mo. | 13 | 12 | 15 | 12 | ... | ... | ... |
| No. of successive days of corticotropin required for adrenal response | 4 | 4 | 4 | 3 | 2 | 1 | 1 |
| Precorticotropin determinations: | | | | | | | |
| Eosinophiles | 243 | 420 | 57 | 153 | 156 | 180 | 258 |
| 24-hr. urinary ketosteroids, mg. | 6.9 | 10.4 | 10.2 | 5.2 | 12.1 | 12.7 | 5.1 |
| 24-hr. urinary corticoids, mg. | 0 | 0.15 | 0 | 0.36 | 0 | 0 | 0 |
| Determinations on day of adrenal response to corticotropin: | | | | | | | |
| Eosinophiles | ... | ... | ... | 39 | 3 | 66 | 30 |
| 24-hr. urinary ketosteroids, mg. | 12.4 | 21.2 | 17.1 | 8.4 | 20.7 | 24.7 | 11.4 |
| 24-hr. urinary corticoids, mg. | 1.4 | 1.4 | 1.2 | 0.9 | 0.2 | 0 | 0 |

* During test period daily doses of cortisone were continued.
† R. A. indicates rheumatoid arthritis.

TABLE 3.—*Data on Subjects Receiving Three-Hour Intravenous Infusions of 25 Units of Corticotropin for Two Successive Days, Followed by Intramuscular Injections of Forty Units of Corticotropin Gel Every Twelve Hours*

| | Patients Treated with Cortisone* | | | | | Controls Untreated with Cortisone or Corticotropin | | |
|---|---|---|---|---|---|---|---|---|
| Name | Lan. | Har. | Pla. | Lou. | Reg. | Ott. | Sul. | Car. |
| Age | 53 | 42 | 54 | 45 | 36 | 64 | 42 | 50 |
| Diagnosis† | R. A. | R. A. | Boeck's Sar. | R. A. | Asthma | A. S. H. D. | Rh. Fev. (Inact.) | Myo. Infare. |
| Daily dose of cortisone, mg. | 50 | 75 | 150 | 62.5 | 37.5 | .. | .. | .. |
| Duration of treatment with cortisone, mo. | 26 | 13 | 20 | 19 | 20 | .. | .. | .. |
| No. of successive days of corticotropin required for adrenal response | 3 | 5 | 4 | 5 | 6 | 1 | 1 | 2 |
| Precorticotropin determinations: | | | | | | | | |
| Eosinophiles | 405 | 108 | 171 | 173 | 341 | 120 | 111 | 159 |
| 24-hr. urinary ketosteroids, mg. | 5.4 | 10.8 | 11.2 | 14.4 | 7.6 | 7.4 | 8.8 | 9.4 |
| 24-hr. urinary corticoids, mg. | 0.2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Determinations on day of adrenal response to corticotropin: | | | | | | | | |
| Eosinophiles | 186 | 33 | 54 | 11 | 0 | 6 | 18 | 63 |
| 24-hr. urinary ketosteroids, mg. | 7.6 | 15.5 | 12.1 | 14.6 | 11.6 | 7.0 | 11.2 | 17.1 |
| 24-hr. urinary corticoids, mg. | 0.8 | 0.9 | 0.6 | 2.1 | 0.6 | 0.5 | 0.9 | 0 |

* During test period daily doses of cortisone were continued.
† R. A. indicates rheumatoid arthritis, and A. S. H. D., arteriosclerotic heart disease.

eosinophiles were counted immediately before and at the termination of the infusion. When corticotropin was given intravenously over a three-hour period, cosinophiles were counted immediately before and three hours following the end of the infusion. With the administration of long-acting corticotropin gel, eosinophiles were counted immediately before and eight hours

3. Pilot, M. L.: Use of Base in Fluids for Counting Eosinophils: A Method for Staining Eosinophils, Am. J. Clin. Path. **20**:870, 1950.

following the morning injection. Urinary 17-ketosteroid determinations were done by the method of Drekter and associates.[4] The 17, 21-hydroxy-20-ketosteroids, hereafter referred to as urinary corticoids, were measured by the Porter-Silber method.[5]

## RESULTS

Initially, 10 patients were given intense adrenocortical stimulation by means of a 16-hour infusion of 25 U. S. P. units of corticotropin daily. A detailed descrip-

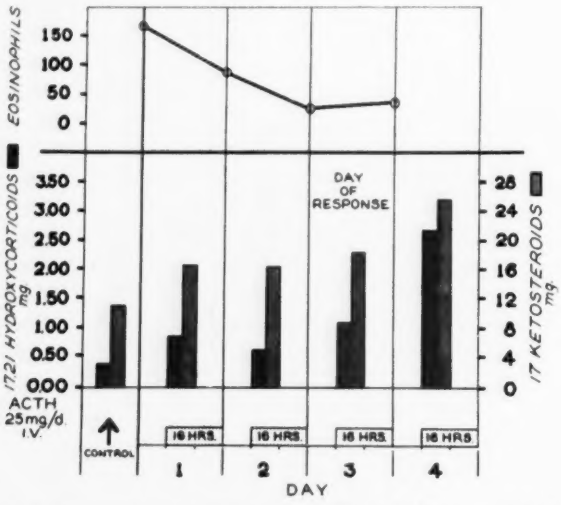


Fig. 1.—Adrenal response to corticotropin (ACTH) given intravenously to Patient Mah., aged 40 years, with rheumatoid arthritis. Cortisone dosage was 75 mg per day for 22 months.

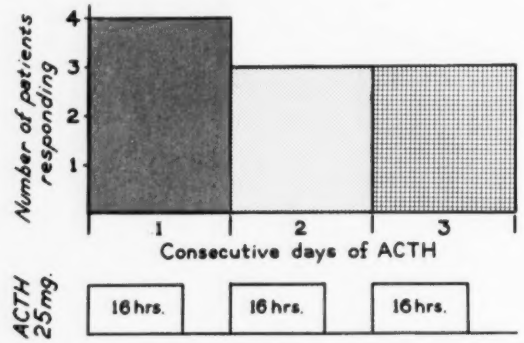


Fig. 2.—Adrenal response to corticotropin (ACTH) given intravenously. Number of patients responding among 10 patients receiving cortisone continuously for 15 to 26 months.

tion of the response of one of these patients is shown in Figure 1. Of the 10 patients who were given daily 16-hour infusions of corticotropin, 4 fulfilled the criteria for adrenal responsiveness on the day of the first infusion of corticotropin (Fig. 2).

4. Drekter, I. J.; Pearson, S.; Bartczak, E., and McGavack, T. H.: A Rapid Method for the Determination of Total Urinary 17-Ketosteroids, J. Clin. Endocrinol. **7**:795, 1947.

5. Porter, C. C., and Silber, R. H.: A Quantitative Color Reaction for Cortisone and Related 17, 21-Dihydroxy-20-Ketosteroids, J. Biol. Chem. **185**:201, 1950.

The remaining six patients showed a delayed adrenocortical response to corticotropin. Two control patients, who received no cortisone, showed satisfactory adrenal response on the day of the first infusion of corticotropin (Table 1).

Inasmuch as 4 of the 10 tested patients showed adrenocortical responsiveness to intense stimulation on the day corticotropin was first administered, it was considered desirable to study the effects of smaller degrees of adrenocortical stimulation. Gordon [6] and Renold [7] have shown that the degree of the effectiveness of adrenal stimulation is diminished as the duration of the intravenous injection is shortened. It has been our experience that in the normal adult the minimal stimulation which consistently produces adrenocortical response results from infusion of 25 units of corticotropin over a three-hour period.[8] Therefore, an additional four patients were given this type of minimal stimulus. In no instance were the criteria of adrenal responsiveness fulfilled after a three-hour infusion of corticotropin daily for two days (Fig. 3). By replacing the less effective 3-hour infusions wtih 16-hour infusions of corticotropin, it was possible to demonstrate adrenocortical responsiveness. Three control patients showed adrenocortical

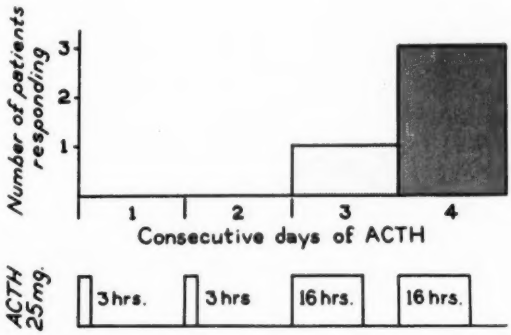


Fig. 3.—Adrenal response to corticotropin (ACTH) given intravenously. Three patients among four receiving cortisone continuously for 12 to 15 months responded by fourth consecutive day of corticotropin administration.

response after the first or second daily three-hour infusion of corticotropin (Table 2). Failure of the treated patients to respond to minimal stimulus with corticotropin is indicative of depression of adrenal function.

A third group of five patients was given 25 units of corticotropin in a three-hour infusion once daily for one or two days, and again adrenocortical function could not be demonstrated (Fig. 4). Long-acting corticotropin gel was then injected intramuscularly in a dose of 40 units every 12 hours. This daily dose of the gel resulted in a cumulative stimulus which was considerably smaller than that produced by the 16-hour infusions, but probably larger than that derived from daily 3-hour infusions.

6. Gordon, E. S.; Kelsey C., and Meyer, E. S.: Adrenal Stimulation by Intravenous ACTH, in Proceedings of the Second Clinical ACTH Conference, Vol. II: Therapeutics, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, p. 30.

7. Renold, A. E.; Forsham, P. H.: Maisterrena, J., and Thorn, G. W.: Intravenously Administered ACTH: A Preliminary Report, New England J. Med. **244**:796, 1951.

8. Krupp, M. A., and others: The Clinical Use of ACTH Intravenously: I. A 3-Hour Test for Adrenocortical Function, to be published.

Of these five patients, one responded on the third successive day of stimulation with corticotropin, one on the fourth, and two on the fifth, while one patient failed to respond until the sixth successive day of corticotropin administration. Three control patients showed adrenocortical response on the first or second day of stimulation by the gel (Table 3). The slow response of the treated patients to an intermediate degree of adrenocortical stimulus bears out the previous indications that adrenal function is depressed.

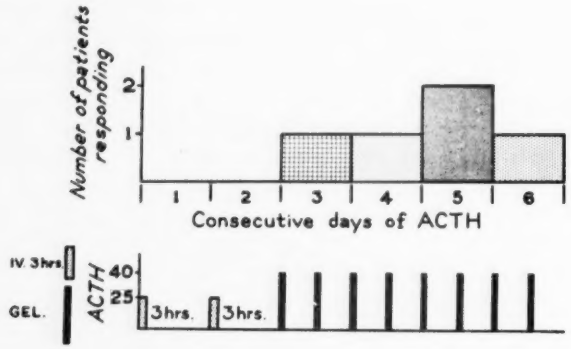


Fig. 4.—Adrenal response to administration of corticotropin gel. Two of five patients receiving cortisone continuously for 13 to 26 months responded in six days of adminstration of corticotropin.

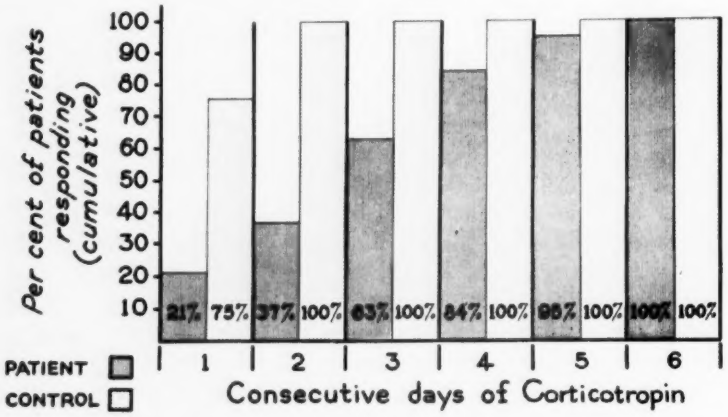


Fig. 5.—Comparison of adrenal response to corticotropin. Nineteen patients received cortisone continuously for 12 to 26 months. Eight patients were controls.

There was no obvious relation between the stimulus required to demonstrate adrenocortical responsiveness and the length of treatment or the amount of cortisone given daily (Tables 1, 2, and 3). A composite survey of our data indicates that adrenal responsiveness was demonstrated in all patients by the sixth successive day of stimulation with corticotropin, despite the continued ingestion of cortisone (Fig. 5).

## COMMENT

It is apparent that the suppression of adrenocortical function which results from continuous, long-term therapy with cortisone is reversible. Furthermore, each of five patients who were subjects of a similar study one year ago showed essentially the same responsiveness they demonstrated in this study (Table 4). Since ultimate adrenal response was shown in these patients, each of whom had received cortisone continuously, there would appear to be no need for interrupted courses of cortisone therapy or alternating courses of cortisone and corticotropin when long-term therapy with cortisone is contemplated.

The fact that most patients required repeated stimulation with corticotropin before adrenocortical response could be demonstrated is further evidence that a dormant state of the adrenal cortex is often induced by cortisone, even by so-called

TABLE 4.—*Adrenocortical Responsiveness to Repeated Administration of Corticotropin at Various Intervals*

| Patient | Year | Mo. of Treatment with Cortisone | Daily Dose of Cortisone, Mg. | No. Successive Days Corticotropin Required for Adrenal Response |
|---|---|---|---|---|
| Mac | 1951 | 4 | 50 | 4 |
| | 1952 | 12 | 62.5 | 2 |
| Mah | 1951 | 14 | 75 | 3 |
| | 1952 | 22 | 75 | 3 |
| Low | 1951 | 4 | 75 | 4 |
| | 1952 | 13 | 75 | 4 |
| Sal | 1951 | 3 | 100 | 4 |
| | 1952 | 12 | 87.5 | 4 |
| B. Phi | 1951 | 7 | 87.5 | 3 |
| | 1952 | 15 | 100 | 4 |

maintenance doses. This emphasizes the need for constant alertness for situations of stress which may necessitate larger doses of cortisone because of the inability of the pituitary-adrenal mechanism to respond spontaneously. Patients receiving cortisone therapy may require additional cortisone during illness or after injury, as do patients with Addison's disease. Moreover, the delay in adrenal responsiveness to corticotropin during treatment with cortisone adds further support to the clinical observation that sudden discontinuance of cortisone therapy may be dangerous. Gradual reduction of the daily oral dose of cortisone before termination of treatment allows the pituitary to resume secretion of endogenous corticotropin, which, in turn, results in recovery of adrenal function.

## CONCLUSIONS

Our studies on adrenocortical function during continuous long-term therapy with cortisone support the following conclusions:

1. Adrenocortical function is suppressed by long-term administration of cortisone, even in "maintenance" doses.

2. Suppression of adrenocortical function induced by cortisone is reversible.

# DIAGNOSTIC AND THERAPEUTIC VALUE OF THE REPRODUCTION OF CHEST PAIN

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WHEN a patient complains of pain in the chest two separate questions often need to be answered. The first involves a decision as to whether or not the pain results from disturbances of the coronary circulation. The second question, which arises only when the first is answered in the negative, involves a positive decision as to the cause of the pain. When a patient is told that his pain is not the result of coronary disease, he naturally wonders what may actually be the cause. Unless this problem can be solved in a manner convincing to the patient, he may continue to believe that the heart is responsible. Such a belief is likely to lead to months or years of unnecessary fright and anxiety on the part of the patient and his relatives.

The purpose of the present article is to emphasize that both of these questions can be answered correctly in most cases provided a few simple procedures are employed in addition to the usual examination. In general, the history must be taken with more care and in greater detail than is usual in regard to precipitating factors. The physical examination of the heart is important because occasionally one will detect aortic stenosis, an ectopic rhythm, or some other abnormality which may be related to the pain. However, in the majority of instances the physical examination of the heart will be negative. In the course of the physical examination certain procedures not commonly utilized, which can be carried out within a few minutes, will in many instances yield the correct answer as to the cause. If upon completion of a meticulous and detailed history and a reasonably careful physical examination, the physician does not either have the complete answer or at least have a strong clue to the answer, it is unlikely that the correct decision as to the cause of the pain will ever be made. If, on the other hand, the history has furnished a clue, it is frequently possible with a few simple office procedures to establish the diagnosis in a way which is not only scientifically satisfying to the physician but which is emotionally satisfying to the patient. It is with such procedures that this article deals.

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In the case of classic myocardial infarction the diagnosis is based largely upon objective criteria. When a patient has evidence suggestive of this lesion, attempts to reproduce the pain are likely to be dangerous. Hence myocardial infarction falls outside the category of the conditions to be considered here.

### REPRODUCTION OF THE PAIN OF ANGINA PECTORIS

Attempts to diagnose angina pectoris on the basis of objective evidence (such as electrocardiograms with the patient at rest, electrocardiograms after standard exercise, electrocardiograms during the breathing of low-oxygen mixtures, and, more recently, ballistocardiograms) have, in our experience, often led to confusion rather than to satisfying information. It is true that an occasional patient whose diagnosis is in doubt and whose electrocardiograms are normal or borderline shows characteristic changes in these records after exercise. However, the amount of exercise required to produce such changes varies widely from subject to subject [1] and frequently from time to time in the same person.

Recent publications would lead one to believe that ballistocardiograms will usually settle this question. It is our impression that the ballistocardiographic technique, while offering great promise of future practical value, has not yet become suitable for routine clinical use. The current methods of recording ballistocardiograms are subject to grave technical discrepancies,[2] and slight differences in technique may lead to well-marked differences in the tracings.[3] Until these difficulties have been overcome, it would seem unwise to draw clinical conclusions from ballistocardiograms.

In the diagnosis of angina pectoris it is essential to establish beyond question that the pain can be produced by conditions which increase sufficiently the discrepancy between the need for oxygen and the supply of oxygen to the heart. The simplest such condition is physical exercise. In most patients with angina the pain can be produced readily by physical exertion. However, the amount of exertion required varies markedly from subject to subject, as would be expected. In attempting to reproduce the pain of angina by exercise [4] certain points should be borne in mind:

1. The exercise should be discontinued as soon as the slightest discomfort occurs.

2. One should bear in mind that the pain of angina pectoris is not the only type of thoracic pain which may be induced by physical effort. Pain arising in the pleura or in the chest wall tends to occur on exercise because the subject breathes more deeply. Likewise, the arms, the pectoral muscles, and the other muscles of the shoulder girdle move with exercise. Hence, pain arising in the skeletal tissues of

1. Sherf, D., and Schaffer, A. I.: The Electrocardiographic Exercise Test, Am. Heart J. **43**:927, 1952.

2. Reeves, T. J.; Willis, K.; Ellison, H., and Booth, E.: Calibration of the Direct Ballistocardiogram, Circulation, to be published.

3. Walker, R. P.; Reeves, T. J.; Willis, K.; Christensen, L.; Pierce, J. R., and Kahn, D.: The Effect of Variations of Recording Surfaces on the Direct Ballistocardiogram, to be published.

4. Theoretically, one would expect such a procedure to be dangerous. Actually, several thousand exercise tests have been performed under our observation and no untoward result has occurred. Granting that a hazard exists, it must be extremely small and, in our opinion, is less grave than the hazard of not knowing whether or not the patient has angina pectoris.

the arms or of the chest wall may be precipitated by exercise. The failure of pain to occur during exercise tends to be of negative diagnostic value, but the demonstration that pain does occur is not necessarily of positive value in the diagnosis of angina pectoris. These points are illustrated in the cases reported hereafter.

3. It should be remembered that the balance between the work of the heart and the coronary blood flow not only depends upon the physical activity of the patient but is conditioned by various other factors, such as the status in regard to meals, the environmental temperature, and the emotional state of the patient. Hence a patient who has had pain only when walking uphill against a cold wind, after a large meal, or after an emotional upset may fail entirely to have pain when exercised in the comparative security of the physician's office. Before one can conclude that the response to exercise is negative, one has to establish the conditions under which the patient has experienced pain spontaneously. In this respect, the following case history is illustrative.

CASE 1.—N. F., a 42-year-old executive, suffered from emotional tension referable to financial affairs. He complained of recurrent episodes of indescribable retrosternal pain of five years' duration. The attacks usually came on after a heavy meal and with exertion such as rapid stair-climbing. He did not relate the individual attacks to periods of emotional stress. Because of a strongly positive family history of coronary artery disease, he had been studied carefully elsewhere. The diagnosis made was mild hypertension, no cardiac disease, and a "cascade stomach." He had been advised to ignore the pain, which had since become increasingly frequent.

A control electrocardiogram was well within normal limits, and there were no significant changes after the combination of a heavy meal and exercise sufficiently violent to accelerate the cardiac rate from 88 to 115 cycles a minute (Fig. 1). No chest pain was produced by insufflation of air into the stomach, although moderate abdominal discomfort resulted. He experienced no chest pain upon running up 80 steps in 35 seconds, after a very large meal, carrying ice in each hand. There was no undue dyspnea and no fatigue associated with this strenuous exertion. At this time it was decided to move the patient from the hospital to his usual environment of work and emotional stress. Three days after he resumed his usual activities a postprandial exercise test, consisting of climbing 52 steps in 90 seconds, resulted in a "squeezing" substernal pain of 90 seconds' duration. Repeat tests on three subsequent days with placebos given sublingually failed to alter significantly this level of exercise tolerance. On three subsequent tests with glyceryl trinitrate 1/100 grain (0.60 mg.) given sublingually five minutes prior to exercise, the stair-climbing tolerance increased to more than 120 steps on each occasion, a rise of tolerance of more than 100%. These data were believed to establish the diagnosis of effort angina, apparently "conditioned" by exposure to the emotional stress of his business, so that coronary insufficiency was present at such times, though not demonstrable even with strenuous exertion when he was hospitalized and relatively free of emotional stress. A ballistocardiogram made at a later date showed low-amplitude complexes, with marked loss of definition of the individual deflections (Fig. 1 *C*). Glyceryl trinitrate, given sublingually prior to anticipated effort, has effectively prevented the pain during the 11 months since the reported examination.

This case illustrates a number of points:

1. The history pointed strongly toward angina pectoris, but the electrocardiogram was normal both before and after exercise.

2. The ballistocardiogram, which was not made until all the clinical studies had been completed, proved to be more reliable than the electrocardiogram in this particular case.

3. Exercise studies should be carried out under conditions similar to those prevailing at the time of the spontaneous attacks. Thus strenuous exertion caused no pain when the patient was mentally at ease. When he was emotionally disturbed

much less exercise regularly induced the discomfort, and this discomfort could be markedly inhibited by glyceryl trinitrate. This patient was unusual in the striking difference between the amount of exercise which could be tolerated without pain when he was emotionally at ease and the relatively slight exercise which produced

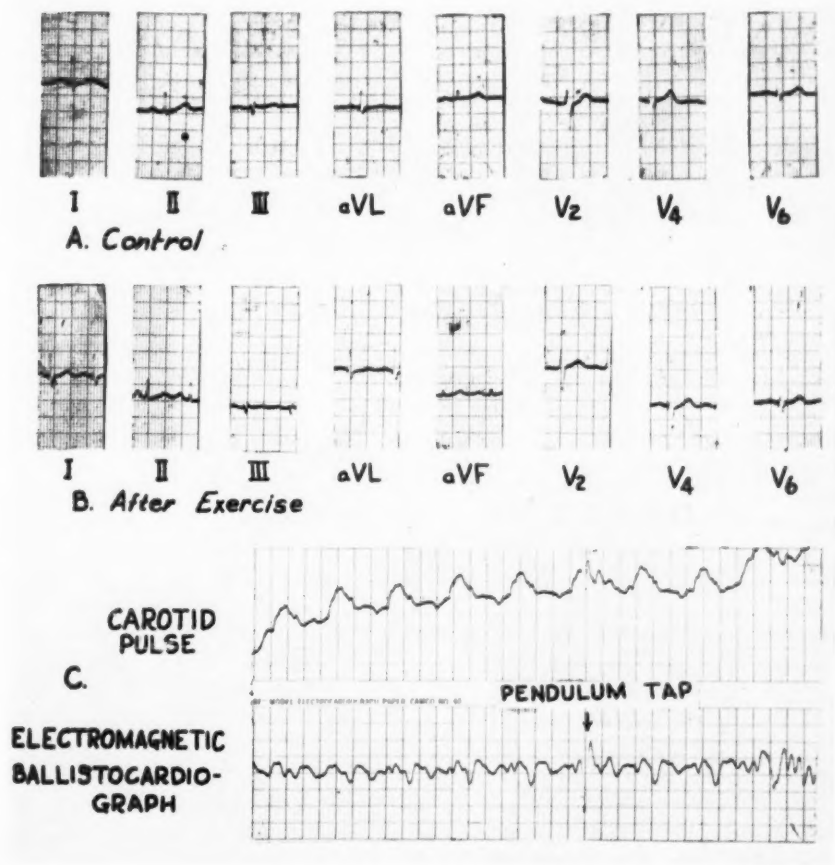


Fig. 1 (Case 1).—The control electrocardiogram (*A*) made with the subject at rest is within normal limits. In the electrocardiogram made immediately after completion of exercise (*B*), although the rate increased from 88 to 115 cycles a minute there were no other significant changes. The ballistocardiogram (*C*) is grossly abnormal in form and amplitude. The expected amplitude of the I-J stroke for a normal subject of the patient's age would be at least 60% of the amplitude of the pendulum deflection, whereas the actual amplitude of the I-J stroke is 20% of the pendulum deflection.

pain when he was emotionally disturbed. However, the unusual feature is only the degree of difference. The general principle has been found to be true in less degree of numerous other subjects.

4. Riseman and Brown [5] observed that glyceryl trinitrate caused a striking increase in the exercise tolerance of patients with angina pectoris. It did so in this patient. This feature has been observed repeatedly in patients with angina pectoris, and we consider it to be of cardinal importance in the diagnosis. In fact, at the present time we are unwilling to make a positive diagnosis of angina pectoris unless two criteria can be fulfilled. The first is that the pain must be reproducible by physical exertion under the proper circumstances with regard to digestion, emotion, and so on. The second is that identical exercise carried out under identical condi-

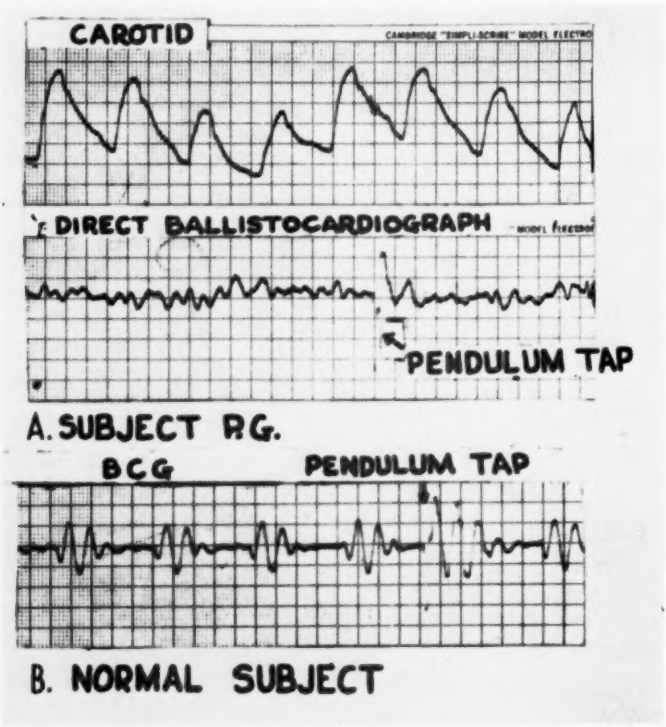


Fig. 2 (Case 2).—The patient's ballistocardiogram (*A*) is of grossly abnormal form. The amplitude of the I-J wave (largest positive systolic deflection) is less than 15% of the standard pendulum deflection. The amplitude of the I-J wave of a normal subject of the same weight (*B*) is 66% of the pendulum deflection. Patient 2, with congestive failure secondary to senile heart disease, illustrates the lack of specificity in ballistocardiographic abnormalities. Any condition resulting in diminution of ejection acceleration will distort the ballistic patterns.

tions after administration of glyceryl trinitrate does not induce the discomfort. The importance of adhering to the latter rule is illustrated by the following case.

CASE 2.—P. G., a 66-year-old man, complained of a peculiar substernal discomfort on exertion, noted over a period of three months. The sensation was described both as a shortness of breath and as a sense of fullness which would become a burning pain if the exertion was con-

5. Riseman, J. E. F., and Brown, M. G.: Medical Treatment of Angina Pectoris, Arch. Int. Med. **60**:100, 1937.

tinued. It was relieved spontaneously after several minutes of rest. The sensation was more frequent and severe during cold and damp weather. No specific activity or motion could be associated with the pain. The patient believed that continued deep breathing shortened the episodes. His physician had prescribed glyceryl trinitrate and visammin (khellin), which the patient stopped taking after no relief was obtained from them.

Physical examination revealed a very apprehensive man with no dyspnea at rest. The lung fields were hyperresonant, and the breath sounds were faint. There were no abnormal cardiac findings. A control electrocardiogram showed somewhat tall and peaked T waves in leads $V_4$ and $V_5$, but was otherwise not remarkable. After climbing 24 steps in 85 seconds, the patient complained of his peculiar substernal discomfort. An electrocardiogram made at this time showed no significant changes. An x-ray of the chest showed pulmonary emphysema, a slightly dilated aorta, and a heart within normal limits of size and contour. A ballistocardiogram was of grossly abnormal form and amplitude (Fig. 2).

Repeated tests after administration of glyceryl trinitrate on subsequent days failed to show significant increase in his exercise tolerance. Of interest is the fact that 1/15 grain of glyceryl trinitrate, taken sublingually, was necessary to produce minimal side-effects in this patient, although the potency of the drug was established in normal subjects. The venous pressure was 370 mm. of saline, and the circulation time, with dehydrocholic acid (decholin®), was 35 seconds. After therapeutic doses of digitalis the exercise tolerance increased to 44 steps in 110 seconds, terminated by fatigue rather than discomfort. He has remained entirely free from chest pain in the three-month period since examination, at an increased level of activity.

On the basis of the history and the ballistocardiogram, this patient was at first considered to represent a classic instance of angina pectoris. However, further investigation failed to support this opinion. It is true that the discomfort could be reproduced regularly by physical effort. However, glyceryl trinitrate, to which the patient was remarkably insensitive, but which finally produced the characteristic pharmacologic reaction, was completely ineffective in altering the exercise tolerance. Subsequent events appear to have confirmed the final impression that the patient did not have angina pectoris but had dyspnea plus chest pain related to pulmonary hypertension.[6] He also had great difficulty in distinguishing between these two symptoms. The important point is that neglect of the criterion that a pain must be responsive to glyceryl trinitrate before it can be considered to be due to angina pectoris would have led to a false-positive diagnosis of angina pectoris in this case.[7] It has been emphasized in a previous publication [6] that pain associated with hypertension in the pulmonary circuit may closely mimic that of angina pectoris, in that it frequently comes on during physical exertion and subsides within a few minutes after the exertion ceases. Furthermore, the location, radiation, and quality of the two pains may be identical. On the other hand, the discomfort associated with hypertension of the pulmonary circuit is not commonly relieved by glyceryl trinitrate. This fact constitutes another reason why it is necessary to observe that the pain is responsive to this drug before considering the diagnosis of angina

6. Viar, W. N., and Harrison, T. R.: Chest Pain in Association with Pulmonary Hypertension: Its Similarity to the Pain of Coronary Disease, Circulation **5**:1, 1952.

7. It is realized that absolute proof of the presence of angina in the first subject, and of its absence in the second subject, rests on clinical judgment alone. Unfortunately, there do not appear to be any methods more accurate than clinical judgment. To rely on evidence obtained at autopsy would be untenable in the light of the demonstration within recent years that angina pectoris may exist with minimal changes in the coronary vessels and may be absent despite the presence of advanced coronary disease. (Blumgart, H. L.; Schlesinger, M. J., and Davis, D.: Studies on the Relation of the Clinical Manifestations of Angina Pectoris, Coronary Thrombosis, and Myocardial Infarction to the Pathologic Findings, with Particular Reference to Significance of Collateral Circulation, Am. Heart J. **19**:1, 1940.)

pectoris to be established beyond question. Apparently, in this case the pain was the result of pulmonary hypertension due to the combination of emphysema and left-sided heart failure.

This case also illustrates the importance of avoiding a specific diagnosis of coronary disease on the basis of the ballistocardiogram. Starr and associates [8] have shown that abnormal records occur with impairment of contraction, regardless of cause.

### REPRODUCTION OF PAIN OF SKELETAL ORIGIN

A large percentage of patients who complain of chest pain and who present no evidence of disturbance of the coronary circulation will be found upon careful examination to have pain arising in the skeletal tissues of the arms or, more commonly, of the chest wall. Some of these patients will show traumatic or arthritic changes in the cervical or thoracic spine on roentgenologic examination. Other subjects will exhibit no such changes. The recognition of the exact site of origin (intercostal muscles, costochondral junction, posterior nerve roots, subcutaneous tissues, and so on) is, in our experience frequently impossible. However, this decision is of academic interest only.

The important question is whether skeletal pain is primary or secondary. The term "primary" is used to refer to a disorder existing without relationship to any organic cardiac disturbance or to any visceral disorder of the chest. The term "secondary skeletal pain" is used to refer to those changes, apparently of reflex origin, which occur so frequently in patients with coronary disease and less commonly in subjects with other visceral disorders of the chest. The "shoulder-hand syndrome," "pseudobursitis," and similar conditions which follow myocardial infarction are classic examples of secondary skeletal pain. Secondary skeletal manifestations often occur in the structures of the chest wall rather than in the arms. Even in the absence of evidence of previous myocardial infarction, they may be present in subjects with angina pectoris. Therefore, demonstration that a patient has chest pain which is undoubtedly arising in skeletal structures should not satisfy the physician. It is also necessary to exclude underlying coronary disease, which in some instances is minimal and can be readily overlooked because it may be masked by the relative predominance of the coexistent pain due to the secondary skeletal disorder. The decision as to the presence or absence of angina pectoris needs to be made by the criteria which have been discussed.

The decision as to whether a pain is of skeletal origin presents few difficulties in most subjects, provided certain simple procedures are carried out. These procedures include compression of the chest in both the anteroposterior and the right-to-left diameter. They include careful pressure on all points of the chest wall, the finger tips being utilized and particular attention being paid to the region of costochondral junctions, which are the most common sites of skeletal pain. Fist percussion of the chest and of the cervical and dorsal spine should be employed. The patient should stand still and swing his arms. When discomfort develops upon walking either on the level or over steps, the walking should be repeated with the arms held rigidly at the sides. Movements of the chest and arms in all directions should be performed with and without resistance. Finally, procaine block of the

8. Starr, I.; Horwitz, O.; Mayock, R. L., and Krumbhaar, E. B.: Standardization of the Ballistocardiogram by Simulation of the Heart's Function at Necropsy: With a Clinical Method for the Estimation of Cardiac Strength and Normal Standards for It, Circulation **1**:1073, 1950.

superficial structures may be of value in differential diagnosis, although this procedure is not specific and may relieve not only skeletal pain but pain arising in the heart as a consequence of myocardial ischemia. These various simple procedures can usually be carried out by the physician within a few minutes at the time the physical examination is being made, and they involve no expense to the patient. They are often more fruitful than all the highly specialized procedures, such as the making of electrocardiograms and ballistocardiograms and x-ray studies. The following case histories are illustrative.

CASE 3.—J. L. S. was an apprehensive 52-year-old white man. Three years previously he had experienced his first episode of chest pain. It was substernal and precordial, constrictive, and not related to position, motion, or respiration. It lasted for several hours. An electrocardiogram led to the diagnosis of myocardial infarction, and he had been treated with complete bed rest for several months. Since that time, although leading an extremely quiet life as a semi-invalid, he had had frequent recurrences of pain. The pain was again substernal and precordial, nonradiating, not affected by position or motion, but occasionally aggravated by cough. It had never been precipitated by exertion. The effect of glyceryl trinitrate on the pain was not known.

Physical examination revealed moderate obesity, hypertension (185/115), and moderate cardiac enlargement.

Review of the electrocardiogram made three years previously, at the time of the initial episode of pain, showed left axis deviation, with a left ventricular strain pattern. The diagnosis of infarction had apparently been made on the basis of a deep Q with inverted T waves in $CF_4$. Electrocardiograms made at the time of our examination likewise showed left axis deviation and the left ventricular strain pattern, with T wave inversion in $V_5$, $V_6$, $AV_L$, and $AV_F$ but no Q wave or loss of R in any of the precordial leads. CF leads, likewise, showed no Q waves, but $CF_4$ recorded with reversed polarity showed essentially the same pattern as the initial electrocardiogram. An exercise test consisting of climbing 44 steps in three minutes resulted in no chest pain, nor was there any significant alteration in the electrocardiogram, although the rate increased from 60 to 80 a minute.

The negative findings at the time of our examination suggested a cause other than angina, and the fact that pain was occasionally aggravated by cough suggested chest wall pain. Subsequently, a careful search for point tenderness resulted in the localization of an area over the left fourth costochondral junction, pressure upon which would precipitate pain exactly similar to the spontaneous attacks. Glyceryl trinitrate did not terminate the attack once initiated, nor would it prevent subsequent pain, which could be regularly produced by pressure.

The significance of the demonstration was immediately appreciated by the patient, who had been incapacitated not by his hypertension, but by his fear of coronary disease.

The major advantage of demonstration of the extracardiac cause of chest pain in this subject was the psychotherapeutic effect. He readily appreciated that a pain which could be produced at will by pressure on the chest wall could hardly be related to heart disease. Thus the major cause of his disability was removed. With his ingrained fear, reassurance on the basis of the other evidence alone could not have been so effective. The costochondral junctions are among the commonest sites of chest pain.

CASE 4.—E. L. B. was a 52-year-old man with the chief complaints of pain in the chest and left shoulder, associated with faintness, occurring infrequently over an eight-year period. The pain was described as a shooting, numbing pain, seeming to originate in the left shoulder and radiating toward the sternum. The intense pain was momentary, but some aching was present for several minutes. The pain had always occurred during activity, such as driving a car, walking, or lifting or reaching for objects. No relationship to meals, emotional tension, fatigue, climate, or other factors could be elicited. The faintness was brief, was relieved rapidly by reclining, and was not preceded or accompanied by palpitation or dyspnea. There was no faintness other than that occurring with the chest pain.

Past history, a review of systems, and family history were not contributory.

The blood pressure was 135/85 with the patient reclining and 130/85 after he stood motionless for three minutes. The thorax was nontender and symmetric. The point of maximal impulse was not palpable. Neurologic examination, including a careful sensory evaluation, showed nothing abnormal.

The resting electrocardiogram was entirely within normal limits. Climbing 40 steps in 60 seconds resulted in no discomfort. The electrocardiogram made immediately after completion of the exercise showed an increased rate from 78 to 115 cycles a minute and a flattening of T waves in $AV_L$, $V_4$, $V_5$, and $V_6$, with a 0.5 mm. depression of the ST segment in II, III and $AV_F$ (Fig. 3). Fluoroscopy of the chest revealed a small heart of normal contour. A systematic review of the individual episodes of chest pain revealed that each of the pains had occurred during activity resulting in some twisting of the body, that is, (1) slipping from a curb causing a near fall, (2) reaching for an inaccessible object far back in a low closet, and (3) twisting to pick up a napkin from the floor. Repeated carotid sinus massage resulted in no faintness or

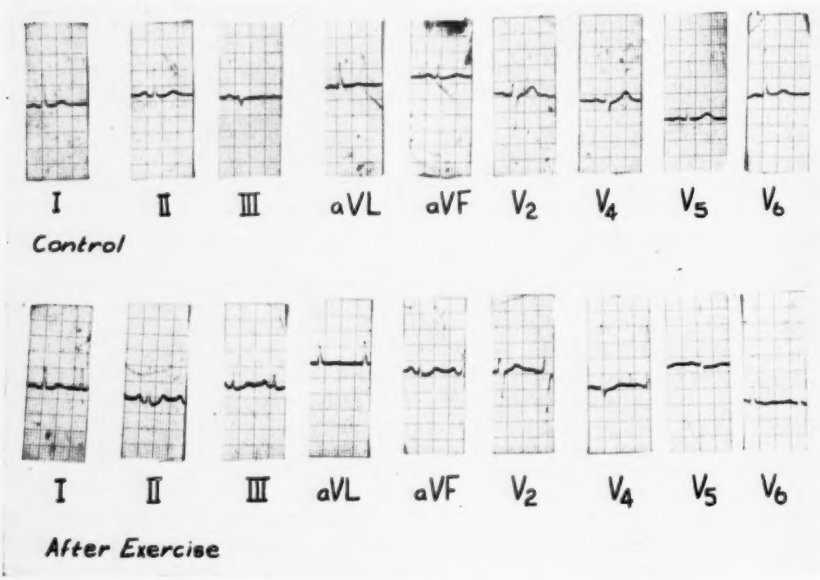


Fig. 3 (Case 4).—The changes in the postexercise electrocardiogram in Leads II, III, $AV_F$, $V_4$, $V_5$, and $V_6$ are indicative of coronary insufficiency by the criteria of some authors. In this case, however, the chest pain arose from a degenerative cervical disk rather than from the heart. We do not accept these electrocardiographic changes as proof of the diagnosis of angina pectoris.

significant alteration in blood pressure. Palpation and percussion of the thorax and spine failed to reproduce the pain. However, with his head turned to the left, attempting to touch his right scapula with his left hand, caused exact reproduction of both the pain and the faintness. X-rays of the cervical spine showed evidence of a degenerated intervertebral disk at a level of the sixth to seventh vertebrae (Fig. 4).

The combination of chest pain on activity with faintness caused an understandable fear of heart disease in this man. The electrocardiogram after exercise revealed definite changes which, however, are not in our opinion outside the expected range for normal subjects within his age group. The chest pain and faintness causing the anxiety were not produced by coronary disease. His ability to reproduce his symptoms precisely by a simple specific motion, while tolerating vigorous exertion

without symptoms, was convincing evidence to the patient of the benign origin of his complaints. Presumably the faintness was of reflex origin due to the painful stimulus.

### THE REPRODUCTION OF PAIN BY HYPERVENTILATION

Whether or not a patient has structural cardiac disease, a belief on his part that such disease exists often induces a state of severe anxiety. This frequently leads to hyperventilation. In most instances hyperventilation causes paresthesias in the extremities or faintness. However, in some patients hyperventilation causes pain in the chest. At times this discomfort appears to be initiated by aerophagia, which often is induced by the augmented respiratory movement. In other instances the

Fig. 4 (Case 4).—X-ray of the cervical spine showing characteristic changes of a degenerative disk at the sixth and seventh cervical vertebrae. The resultant root compression with the patient in specific positions caused chest pain and faintness.

increased muscle tension resulting from carbon dioxide deficiency may lead to pain in the chest. Such pain is occasionally unilateral and confined to the left side. Its occurrence increases the anxiety, which in turn aggravates the hyperventilation. It is not entirely clear why unilateral and asymmetric discomfort develops in some patients when one would expect that symptoms resulting from a chemical abnormality of the blood would be bilateral. In some instances local conditioning factors such as arthritis have been found to be present, and it is believed that these tend to sensitize local muscle areas. However, in other subjects no such localized conditioning factors have been found, and the reason for the unilateral appearance of discomfort remains obscure.

The following case summary illustrates chest pain consequent to hyperventilation.

CASE 5.—G. O. S. was a 34-year-old man in excellent health until rejection by the army 12 years prior to the present examination. He was told that he had high blood pressure and "something peculiar" about the cardiac findings. Subsequently, he noted recurrent episodes of moderately severe chest pain, generally aching but sometimes cramping with accentuations of sharp striking pain. The duration of each episode varied from 60 minutes to several hours, with a totally irregular frequency of attacks, which occurred during exertion and at rest. There was no respiratory aggravation, and no dyspnea was noted at any time. Approximately six months before the present examination the pain became more severe and more frequent, and at this time the patient noted a dull aching pain in both wrists, with a sensation of numbness sometimes extending to the elbows. These symptoms usually were concomitant with the chest pain but on a few occasions were noted independently. A physician consulted at this time told him that the pain was "anginoid" and prescribed glyceryl trinitrate, which did not relieve the pain. The patient had found that 2 oz. of whisky would relieve both symptoms. He had greatly limited his physical activity because of concern over the significance of, rather than the discomfort caused by, his chest pain.

The patient was tall and moderately obese. His blood pressure when reclining was 150/80. No skeletal or muscular tenderness was elicited upon careful search for trigger areas. The heart was not enlarged, and there were no thrills, murmurs, or unusual sounds. There was no evidence of neurologic disturbance and particularly no alteration of sensory modalities of the arms.

The electrocardiogram revealed low T waves in $AV_L$ and $AV_L$, with a semihorizontal heart. Violent exercise—taking 72 steps up in two minutes—was well tolerated, without any discomfort in the chest. Ballistocardiograms made with the direct technic were of normal amplitude and contour.

The patient was then deliberately caused to hyperventilate during auscultation of the chest, with the spontaneous complaint of pain in his chest and arms identical with his previous attacks. Repetition of hyperventilation again resulted in similar symptoms. The reassurance given to this patient was readily acceptable after explanation of the physiologic disturbances induced by hyperventilation.

The history of chest pain and arm pain in a moderately obese man, coupled with some deviation from usual electrocardiographic patterns, was thought at first to be suggestive of angina pectoris. However, the demonstrated excellent tolerance to vigorous exertion, and the failure to obtain even partial relief from glyceryl trinitrate militated strongly against a diagnosis of coronary disease. The low voltage of the T waves was believed to be due either to an unusual but normal position of the heart or to hyperventilation.

### REPRODUCTION OF PAIN ARISING FROM THE STOMACH AND FROM THE SPLENIC FLEXURE

It is well known that disorders of the lower part of the esophagus and the proximal portion of the stomach may give rise to pain resembling in many respects that due to coronary disease. Thus hiatal hernia, cardiospasm, and, less commonly, diverticulum of the esophagus, diverticulum of the stomach, or cascade deformity of the stomach may produce such pain. Likewise, patients with pylorospasm associated with gall-bladder disease or with peptic ulcer may have pain in the chest. More frequent, however, are subjects with pain arising in the stomach but felt in the chest in whom no abnormality of the stomach or gall bladder can be demonstrated by x-ray investigation. Apparently, these persons swallow air and have increased tone of the pylorus, so that the stomach tends to become distended with air. Some have pain in the epigastrium, but a considerable proportion notice their

discomfort in the chest. The recognition of chest pain due to this cause cannot be accomplished by roentgenologic investigations of the gastrointestinal tract. A simpler and less expensive procedure will usually solve the problem. This procedure consists of the insertion of a tube into the stomach and distention of this organ with air. The test is positive only when the spontaneous pain of which the patient complains is exactly reproduced. One can produce discomfort in any one by this procedure, which is significant only when the patient's individual discomfort is reproduced. The following case history is illustrative.

CASE 6.—P. L., a 42-year-old plumber, was in excellent health until six months prior to consultation, when, while engaging in vigorous exertion, he noted a sense of fullness in the upper abdominal and lower substernal areas. Simultaneously, he noted a rapid regular palpitation, gradually increasing in rate. Both symptoms were slightly relieved by belching, but both took several hours to subside completely.

On the following day physical examination revealed no evident changes from his usual findings, but an electrocardiogram was interpreted by a specialist in a neighboring city as showing changes indicative of myocardial infarction. This opinion was based on a rather deep Q in Lead III with inverted T waves, plus questionable ST segment deviation. Subsequent tracings showed marked changes in QRS and T patterns "compatible with evolution of infarction." The patient was kept in bed for several weeks and then gradually returned to limited activity. Since that time he had had frequent recurrences of substernal and upper abdominal discomfort, with palpitation, occurring usually with postprandial exertion. Glyceryl trinitrate had failed to give any relief.

The physical findings were not abnormal, other than blood pressure measurements of 135/90 on several occasions. The heart was not enlarged, the rhythm was regular, and there were no murmurs.

The electrocardiogram showed marked variation of the complexes in Leads III and $AV_F$, with different phases of respiration, but was otherwise not abnormal. During quiet breathing there was a QR, the Q being 25% of R, and the T wave was isoelectric. With deep inspiration the Q almost disappeared and the T wave became upright, while with deep expiration the Q became 50% of R, with the T wave inverted. The latter pattern was strikingly similar to the one interpreted as myocardial infarction at the time of his initial pain. Climbing 72 9-in. steps in three minutes did not result in chest pain. The stomach was then distended with 1,500 ml. of air via a Levin tube, the procedure resulting in exact reproduction of his spontaneous attack of chest pain and palpitation. Both symptoms were terminated abruptly by withdrawal of the air. An explanation of the benign nature of the pain, plus atropine therapy, produced dramatic relief of pain and apprehension.

Failure to recognize the possibility of diaphragmatic positional variations in the electrocardiogram as a cause of the changes noted at the time of this patient's initial examination resulted in an erroneous diagnosis of myocardial infarction. Consequently, a deep-seated conviction of heart disease had been implanted in him. The demonstration of the patently benign cause of his pain was of definite value in helping him to overcome this fear.

Not only the stomach but occasionally the splenic flexure may be the seat of pain which is felt mainly in the chest. In such an instance the patient will often give a history of having less discomfort immediately after a bowel movement and of having more when constipated. Furthermore, there will occasionally be a statement that the pain is instantly and dramatically relieved by the expulsion of flatus. When these clues exist, a suspicion of the splenic-flexure syndrome should arise, and a direct test should be made by inserting a tube high through the rectum and inflating the splenic flexure. In this case, as in the case of air in the stomach, a positive test consists not in producing pain but in reproducing the exact pain of which the patient complained. The following case history is illustrative.

CASE 9.—Mrs. P. S., aged 36, had experienced attacks of paroxysmal auricular tachycardia for 10 years. Precipitating factors were apparently fatigue, emotional crises, and possibly spontaneous hypoglycemia, since most of the attacks occurred three to four hours after meals. She could instantly terminate most attacks by a Valsalva maneuver. During the same period she had noted attacks of shortness of breath of brief duration, preceded usually by emotional disturbances. The shortness of breath frequently preceded the episodes of palpitation and were terminated abruptly with the termination of tachycardia. There was some faintness associated with the dyspnea but no other symptoms of tetany or respiratory alkalosis. During the three months before examination she had experienced three episodes of stabbing, burning pain of moderate severity in the left lower chest. The pain came in waves of one to three minutes' duration, over a period of one to two hours. All the attacks had occurred two to four hours after the evening meal, before the patient retired. Pain was aggravated by the sitting position and relieved completely in stepwise fashion by the repeated passage of flatus. These attacks were not accompanied by palpitation but were preceded by a mild sensation of shortness of breath.

Physical findings were not abnormal. The blood pressure was 125/75. There were no physical evidences of structural heart disease, and no evidence of thyrotoxicosis was noted. No tenderness was elicited over the chest or abdomen.

The electrocardiogram was entirely normal. Fluoroscopy of the chest revealed a small, vertical heart of normal contour. The lung fields were clear, and diaphragmatic excursion was normal.

With the patient recumbent, 650 mm. of air was injected through a rectal tube placed approximately at the splenic flexure. The insufflation resulted in extreme pain over the lower abdomen. After assuming the sitting position for a period of two to three minutes, she experienced a severe pain over the left precordial area of the same quality as the spontaneous episodes previously noted. Fluoroscopy with the patient seated revealed air in the splenic flexure. Compression of the abdomen over this area to displace the air headward caused aggravation of the pain, which was relieved by removing the pressure.

Deliberate hyperventilation resulted in the same sensation of faintness she had described in the attacks of shortness of breath.

In this patient the initial factor in causing the anxiety state was the presence of paroxysmal auricular tachycardia. Despite repeated assurance as to the benign nature of this disorder the patient was not convinced and believed that she had serious heart disease. When pain subsequently developed in the anterior portion of the left lower chest, she became even more certain that serious cardiac disease was present. The result was the development of a severe and disabling anxiety state. After the pain had been exactly reproduced by distention of the splenic flexure, the patient was convinced that the discomfort was of minor nature and due to "gas." The anxiety state, therefore, disappeared in large measure. She continued to have severe fright during the attacks of paroxysmal tachycardia, but otherwise was able to lead a normal life and was no longer a psychic invalid.

### DISCOMFORT ARISING FROM THE INTRATHORACIC VISCERA

The pleura, pericardium, and mediastinum are common sources of chest pain. During the course of respiratory infection, and in some subjects for some weeks after such an infection, there is likely to be a minimal sensation of substernal pressure, sometimes associated with sharp aggravation during deep breathing, swallowing, or yawning. This sensation is probably to be ascribed to swelling of the mediastinal lymph nodes, as it resembles in quality but not in intensity the discomfort observed in persons with Hodgkin's disease or carcinoma of the lung with metastasis to the mediastinal glands. Patients with spontaneous pneumothorax or with mediastinal emphysema may have severe pain. Pain produced by these conditions may resemble that due to myocardial infarction or to angina pectoris but

has one important difference. The relation to respiration is much more striking. In patients with angina pectoris respiratory aggravation is conspicuous by its absence. Patients with myocardial infarction who have pericarditis may notice respiratory aggravation, but this is rarely striking and usually does not appear until the pain has been present for some hours. On the other hand, patients with pericarditis, pleurisy, mediastinal lymphadenitis, mediastinal emphysema, or spontaneous pneumothorax are likely to have pain in which respiratory aggravation is present from the beginning and is marked. Therefore, the effect of deep breathing and of holding the breath in various respiratory positions should be tested in every subject with chest pain. Demonstration that the pain is aggravated by respiratory maneuvers will practically exclude angina pectoris, except in so far as patients with angina pectoris may have increased tension in thoracic muscles and the discomfort directly referable to these muscles may be aggravated by the respiratory maneuver.

The condition which simulates angina pectoris more closely than any other is that which has been called "hypercyanotic angina" or "pulmonary hypertensive pain."[9] Patients with this condition frequently have pain with effort. The location, quality, and duration may be identical with the discomfort of angina pectoris. However, the electrocardiographic changes, when present, are usually those of right ventricular strain, and the pain does not usually display the same relationship to glyceryl trinitrate as does the pain of angina pectoris. A number of cases of pain of this type have recently been reported,[6] and our Case 2 illustrates this type of discomfort. Here the reproduction of pain by exercise and the demonstration that exercise tolerance is not increased by glyceryl trinitrate are of major diagnostic import.

## COMMENT

*Diagnostic Considerations in the Reproduction of Chest Pain.*—The emphasis placed in this article on the diagnostic value of reproducing the patient's pain should not be interpreted as indicating a lack of appreciation of more objective methods. In patients so ill as to require hospitalization objective findings will often be the most reliable indications of the cause. However, the vast majority of patients with pain in the chest are ambulatory, and in many cases the most careful study by electrocardiogram, ballistocardiogram, and x-ray will fail to yield positive information as to the cause of the pain. It is in such cases that the diagnosis can often be readily established after other means have failed by procedures which reproduce pain. It is neither practical nor desirable to attempt to utilize all of the various procedures for reproduction of pain in an individual case. Discrimination is needed in the choice of procedure to be employed. The clue must come from the history in most instances and particularly from those aspects which deal with the relationship of the pain to body functions which tend to aggravate or alleviate it. In order to avoid overlooking the historical clue it is necessary that a systematic plan of questioning be employed. A suitable questionnaire is illustrated in Appendix 1. No especial virtue is claimed for this particular questionnaire. The point is that a systematic method of questioning must be employed and that the symptom must be analyzed in great detail if the clue as to the necessary procedure is to be obtained.

Once a suspicion has been aroused that the pain is arising in a certain area, such as the chest wall, stomach, splenic flexure, or coronary vessels, the procedure of choice will be obvious from the examples which have been cited. In carrying out

9. Vicar and Harrison.[6]

the various procedures certain technical points are of importance, and these are considered in some detail in Appendix 2.

It should be emphasized again that we are concerned here not with producing chest pain but rather with reproducing the exact pain of which the patient complains. The procedural tests should be considered negative when they induce discomfort which bears no relationship to the spontaneous discomfort. It is only when the spontaneous pain has been reproduced in location and quality that the test may be considered positive. Obviously, exact reproduction of intensity is not to be expected.

*Therapeutic Considerations in the Reproduction of Chest Pain.*—Two points may be mentioned here. When the patient does have angina pectoris, reproduction of the pain by threshold physical effort and demonstration that the same effort does not cause the pain when undertaken immediately after administration of glyceryl trinitrate tends to induce a feeling of confidence in him. This confidence extends both to the physician and to the drug. It helps to alleviate the anxiety which is such a distressing feature in many patients with coronary disease.

When, on the other hand, the investigations indicate clearly that the patient does not have angina pectoris but is suffering from pain in the chest from some less serious disorder, the reproduction of the pain is of even greater therapeutic importance. The patient's anxiety is likely to be totally unnecessary. Nevertheless, it often persists despite the most emphatic reassurance on the part of the physician when such reassurance is based only upon negative evidence and when the patient has not experienced the discomfort in the physician's presence. But when the physician has demonstrated to the patient that he can induce the discomfort at will and can relieve it at will the patient tends to experience relief. He reasons that a doctor who can produce and alleviate the pain must understand it. Therefore he is more ready to accept the physician's statement that there is no serious cardiac disease and that the pain is due to the other and minor disorder. It is simply a case of the physician's actions speaking louder to the patient than the physician's words.

The securing of a detailed and meticulous history is a time-consuming affair. Carrying out the various procedures which have been illustrated in this article also requires considerable time. It is much quicker to take an x-ray or an electrocardiogram and then guess about the cause of the pain than to take the trouble to find out its exact cause. On the other hand, the emotional distress of many patients with chest pain is so great that one is justified in spending all the time required to establish the exact diagnosis and to alleviate unnecessary anxiety.

Pain in the chest is often related by the patient to serious heart disease and to the prospect of sudden death. Despite strong reassurance, a diagnosis of coronary disease frequently aggravates this fear to such an extent that almost every waking moment is spent in apprehension of the next. The patient not uncommonly confesses to a dread of sleep "because I might not wake up." The tragedy of such a diagnosis, correctly made, is multiplied many times when an innocuous cause of the pain is misinterpreted as coronary disease. When considered in the light of total suffering involved, it becomes apparent that a false-positive diagnosis of coronary disease is usually a greater error than overlooking the disease when it is present. When errors are made they should be on the side of optimism.

The diagnostic and therapeutic advantages of reproducing pain in the chest have been illustrated by a number of case histories. The following considerations are believed to be particularly significant:

1. The diagnosis of angina pectoris is usually doubtful unless two criteria are met.

(*a*) The pain should be reproducible by physical effort under appropriate conditions in regard to emotional stress, meals, and so on.

(*b*) It should be demonstrated that the same physical effort carried out under the same conditions does not cause the pain when undertaken a few minutes after administration of glyceryl trinitrate.

2. When these criteria are followed, angina pectoris will be found to be present in a certain number of patients in whom this disorder is overlooked when more objective criteria of diagnosis are used. Similarly, patients who would otherwise have a false-positive diagnosis made on the basis of minor electrocardiographic changes will be found to be free of angina, according to these criteria.

3. When angina pectoris has been excluded, recognition of the cause of the pain will often be aided by reproducing the pain. The procedure to be utilized will depend on the clues obtained from a detailed history. Among such procedures are pressure on the chest wall, special movements of the chest or arms, hyperventilation, and distention of the stomach or colon with air.

4. Anxiety is becoming the most important of all symptoms of persons with cardiac disease or with the suspicion of cardiac disease. One of the most effective methods of alleviating unnecessary anxiety is the reproduction of the patient's pain. When coronary disease is not responsible the patient is more likely to accept the physician's statement that the cause is innocuous if the physician has been able to reproduce the pain at will.

## APPENDIX 1: SYMPTOM QUESTIONNAIRE FOR PATIENTS WITH CHEST PAIN

I. *Location of pain:*

1. Area of maximal intensity?.....
2. Regions of less intensity?.....
3. Radiation of pain (area and rank)?.....
4. Areas of tenderness to light touch?.....
   to firm pressure?.....(Give regions.)

II. *Duration of pain:*

1. Since it first began.....
2. Of individual attacks.....

III. *Intensity of pain* (underline one or more): Minimal, mild, moderate, severe, very severe, excruciating.

IV. *Quality of pain* (underline all appropriate words): Steady, intermittent, striking, stabbing, cutting, shooting, burning, squeezing, pressing, fullness, cramping, aching, throbbing, gnawing, drawing, tearing, pulling, indescribable.

V. *Environment* (encircle factor causing any change in condition and insert W if worse, or B if better, in accompanying space): Winter...., spring....., summer....., fall....., wet weather....., dry weather....., dust....., high altitudes....., work days....., week ends....., day....., night.....

VI. *Relation of pain to body functions* (insert B if better, and W if worse):

1. Position:

   A. Lying down....., right side....., left side....., prone....., supine.....
   B. Sitting upright....., leaning forward....., leaning back.....

C. Standing.....

If better or worse in certain positions, does the improvement or aggravation come on instantly....., rapidly (within a minute or two)....., or gradually.....?

2. Physical exertion:

A. Is the pain brought on by slow walking on the level....., rapid walking on the level....., walking uphill....., stair climbing....., any vigorous exercise .....? If so: (1) does it set in instantly (with the first step)....., or only after walking..... distance? (2) Does it cease instantly when exertion is stopped..... or gradually after..... minutes? (3) Is the pain brought on by swinging the arms without walking....., walking without moving the arms ..... (has the pain ever occurred while you were walking with hands in pockets.....), rapid or deep breathing without walking....., holding the breath.....? (4) Is the exertion more apt to cause pain when you are tired after a day of stress.....?

B. Is the pain initiated (I) or aggravated (A) by specific muscular movements, such as bending the body....., raising arms....., picking up heavy objects ....., any other.....?

3. Respiratory function:
Is the pain made better (B) or worse (W) by holding breath....., ordinary breathing....., sudden deep breath....., continued rapid panting....., coughing....., sneezing....., laughing....., yawning.....?

4. Alimentary functions:

A. Is the pain made better (B) or worse (W) by chewing....., swallowing....., eating....., belching....., bowel movements....., flatus.....? Indicate whether effect is instantaneous (I) or gradual (G).

B. Is the pain most apt to occur (O) or has it never occurred (N) after eating ....., within the first hour after eating....., within two hours after eating ....., more than four hours after eating.....?

5. Emotional functions:

Is the pain initiated (I) or aggravated (A) by worry, anxiety stress....., anger ....., pleasant excitement....., sexual intercourse.....?

6. Menstrual periods:

Is the pain more apt to occur during the week preceding onset of flow....., during menstruation....., with no relation.....?

VII. *Additional information relative to pain:*.....

*Summary:* .....

## APPENDIX 2: METHODS EMPLOYED IN THE REPRODUCTION OF CHEST PAIN

A. *Glyceryl Trinitrate-Exercise Test.*—Under conditions individually standardized for each subject, referable to emotional state, meals, time of day, and so on, exercise consisting of climbing stairs at a constant rate (number of steps climbed a minute) is performed before and after the sublingual administration of glyceryl trinitrate. The climbing may be done on a "two-step box" or a convenient flight of stairs. The exercise should be continued each time until minimal pain is noted in the chest or arms and then immediately discontinued. The test should be terminated before undue dyspnea or fatigue occurs. The patient should be carefully instructed regarding the importance of the factor of minimal pain as an "end point" to the test. The control level of exercise tolerance should be determined by at least three separate tests, preferably with the use of sublingually administered placebos to exclude the factor of suggestion. Soluble saccharin tablets are readily available and satisfactory placebos. The interval between tests should be at least 30 minutes in order to minimize the known phenomenon of increased coronary flow resulting from the initial excercise and should preferably be done on different days. An

increased tolerance to the exercise following administration of glyceryl trinitrate should be verified on repeated tests. A schedule which has been found to be reliable is as follows:

| Test | Day | Time, Min. | Drug | Steps | Time |
|---|---|---|---|---|---|
| 1 | 1 | 0 | 0 | x | x |
| 2 | 2 | 60 | Placebo | x | x |
| 3 | 3 | 120 | Glyceryl trinitrate | x | x |
| 4 | 2 | 0 | Glyceryl trinitrate | x | x |
| 5 | 2 | 60 | Placebo | x | x |
| 6 | 2 | 120 | 0 | x | x |

An evaluation of exercise performed under each condition should make possible a positive decision as to the effect of glyceryl trinitrate. The test is considered positive only if a significant increase in the exercise performance is noted after administration of glyceryl trinitrate. A positive test is considered strong evidence for a diagnosis of angina pectoris.

B. *The Reproduction of Chest Pain of Skeletal Origin.*—This has been discussed in the text.

C. *Reproduction of Chest Pain Precipitated by Hyperventilation.*—The induction of a satisfactory level of respiratory alkalosis by hyperventilation is not always easily accomplished. It has been found that such a level may be reached most easily under the guise of careful and prolonged auscultation of the chest, the subject being asked to respire at a maximal rate for several minutes. He should be constantly urged to breathe with more depth and vigor, since the natural tendency is to decrease respiration after minimal symptoms are noted. If the test so performed is negative, then the subject should be informed that the effect of deep breathing is to be studied, and deliberate hyperventilation should be performed. It must be realized that several minutes of acute hyperventilation may be necessary to create levels of respiratory alkalosis. A patient may attain spontaneous hyperventilation for several hours.

D. *Reproduction of Chest Pain Arising from Abdominal Viscera.*—If the history suggests that the pain is worse after meals, is affected by positions causing increased intra-abdominal pressure, and is relieved by eructation, the stomach should be distended with air. This may be done by injecting the required amount of air, usually 1,000 to 1,500 ml., through a tube previously passed into the stomach. The injection is most efficiently done through a three-way stopcock with a 50-ml. glass syringe. The positions should be altered as suggested by the history and should include both lateral reclining positions as well as the supine positions. Sitting up and leaning forward frequently precipitates the discomfort. Pressure by hand should be exerted in various directions to increase focal intra-abdominal pressure. It must be remembered that the only valid criterion is exact qualitative reproduction of the patient's spontaneous discomfort. If the pain is reproduced, air should be withdrawn through the tube, with rapid relief expected. The procedure should be repeated to satisfy doubt of the patient or physician.

If these maneuvers do not reproduce the symptoms, particularly if there is a history of relief by the passage of flatus or by stool, and if the pain is aggravated by lying on the right side and relieved by changing the position, distention of the colon is indicated. This is done by passage of a lubricated rectal tube to approximately the splenic flexure. It is desirable, but not necessary, to verify this position by fluoroscopy. Air is then introduced via suitable adapters, by a syringe and stopcock, until discomfort is noted by the patient. Position and pressure should be varied as with the gastric distention and the same criterion observed.

# SINOAORTIC REGULATORY SYSTEM

## Role in Pathogenesis of Essential and Malignant Hypertension

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WHILE most authors agree on the humoral nature of renal hypertension, at least in early stages, there are many different theories concerning the pathogenesis of essential hypertension. The most important of these theories are vascular sclerosis, humoral mechanism, renal ischemia, hypoxemia of the brain, and hypersensitivity of the vasoconstrictor centers. Page [1] wrote that hypertension is the result of multiple forces acting on the circulatory apparatus and that the problem cannot be solved in the elucidation of only one of these forces. Page tried to integrate all the presently known etiological factors into one system.

Since the discovery of the aortic nerve by de Cyon and Ludwig and of the carotid nerve by Hering, investigators have learned from numerous animal experiments that these nerves are most sensitive to minute changes in blood pressure. Physiologists Hering, Koch, and Heymans proposed, therefore, that essential hypertension may develop through disruption of the receptors of these nerves due to sclerosis of the arterial walls. Most of the later authors have denied the role of the sinoaortic regulatory system in the pathogensis of essential hypertension because neurogenic hypertension, which may be obtained by resection of the carotid and aortic nerves in animals, differs in its circulatory mechanism from essential hypertension.[2]

Czermak observed that pressure on the carotid bulb resulted in bradycardia. Many years later clinicians developed a carotid sinus pressure test and studied differences in the response to this test of normal and hypertensive patients. Extensive studies of Möller [3] showed that the depressor response to carotid bulb pressure increased gradually with age and that in hypertensive patients there was the same increase, except that it appeared in an earlier age group. He concluded from this that the receptors in the carotid sinus were not disrupted in hypertension

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1. Page, I. H., and Corcoran, A. C.: Arterial Hypertension: Its Diagnosis and Treatment, Chicago, Year Book Publishers, Inc., 1945; Pathogenesis of Arterial Hypertension, J. A. M. A. **140**:451-458, 1949.

2. Nickerson, M.: Sympatho-Adrenal Factors in Hypertension, in A Symposium Held at the University of Minnesota on Sept. 18-20, 1950, in honor of E. T. Bell, B. J. Clawson, and G. E. Fahr, Minneapolis, University of Minnesota Press, 1951, pp. 150-160.

3. Möeller, E.: Der Karotisdruckversuch beim Normalen, bei der Hypertonie und anderen veränderten Kreislaufeinstellungen im Zusammenhang mit der reflektorischen Selbststeuerung, Arch. Kreislaufforsch. **10**:185-209, 1942.

and their function was unimpaired. Hering,[4] however, showed the inaccuracy of the pressure test on the carotid bulb. He observed that young patients who have no response to external carotid sinus pressure show a definite drop of blood pressure and bradycardia when the carotid bulb is stimulated directly during an operation for removal of goiter. It is evident that the anatomical site of the bulb prevents adequate mechanical stimulation externally.

None of the presently supported and above-mentioned theories of the pathogenesis of essential hypertension considers one of the most fundamental questions in hypertensive research: Why is the elevation of blood pressure in hypertension not counteracted by the depressor reflex which is initiated by the carotid sinus and aortic nerves?

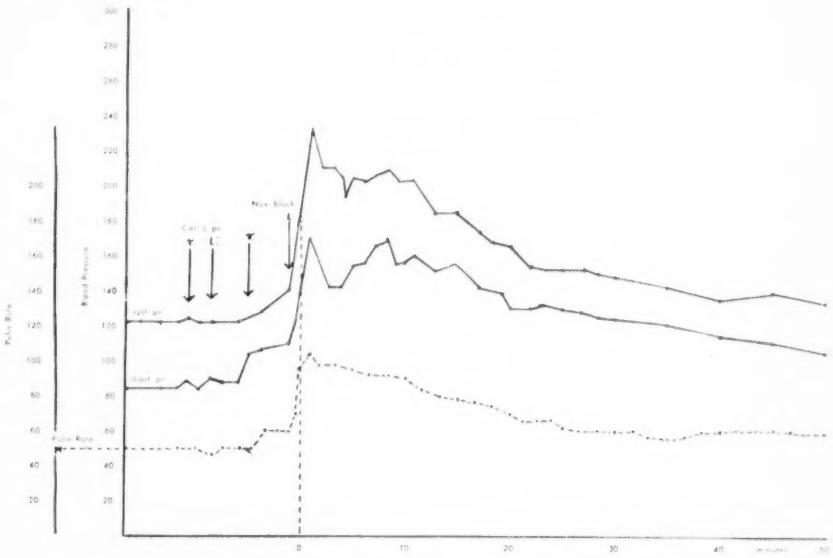

Fig. 1.—Graph showing results of procaine (novocaine®) hydrochloride block of carotid sinus in patient with normal blood pressure. *Nov. block* means novocaine® block; *Car. s. pr.*, carotid sinus pressure; *syst. pr.* and *diast. pr.*, systolic and diastolic pressure, respectively. *R.* and *l.* indicate right and left.

## PROCAINE BLOCK OF THE CAROTID SINUS

Because of the importance of this question, a more accurate test of carotid sinus function was devised, using procaine hydrochloride block rather than stimulation by external pressure. It is known from many animal experiments that after section or block of the carotid sinus nerves high blood pressure and an increased pulse rate always develop. This is termed neurogenic hypertension. The level of this hypertension is characteristic for each animal species. To determine the human response to bilateral carotid sinus block, a relatively accurate method of procaine block was developed and has been reported elsewhere.[5]

4. Hering, H. E.: Die Karotissinusreflexe auf Herz und Gefässe vom normal-physiologischen, pathologisch-physiologischen und klinischen Standpunkt: gleichzeitig über die Bedeutung der Blutdrückzügler für den normalen und abnormen Kreislauf, Dresden, Theodore Steinkopff, 1927.

5. Lampen, H.; Kezdi, P., and Kaufmann, L.: Entzügelungschockdruck am Menschen, Klin. Wchnschr. **27**:272-278, 1949.

In 14 patients without cardiovascular disease and in normal volunteers the bilateral carotid sinus block with procaine resulted in an average blood pressure elevation of 80 mm. systolic and 55 mm. diastolic and a pulse rate increase of 53 beats per minute. The initial peak lasted about five minutes and was followed by a gradual decline. The original level in pulse rate and blood pressure was reached again in 50 to 60 minutes. In some subjects, however, there was a more rapid drop to a medium level, followed by a secondary rise and then a gradual decline to the original level. (Figure 1 shows a typical graph for a normotensive patient.) Patients with essential and malignant hypertension were next examined by this technique. The results have been published in detail elsewhere.[6] Nine patients with essential hypertension showed an average blood pressure rise of 82 mm. systolic and 45 mm. diastolic and a pulse rate increase of 51 beats per minute. Six patients having malignant hypertension were studied. The average blood pressure rise was 101 mm. systolic and 53 mm. diastolic, with a pulse rate elevation of 50 beats per minute. The average values of the peak levels for blood pressure and pulse rate elevation following procaine block of the carotid sinus in normotensive and hypertensive patients are given in Table 1. An example of response to carotid sinus block in essential hypertension is seen in Figure 2, while response in malignant hypertension is illustrated in Figure 3. There is an interesting difference between the curves for normotensive and for hypertensive subjects

TABLE 1.—*Averages of Blood Pressure and Pulse Rate Elevation in Normotensive and Hypertensive Patients Following Procaine Block of Carotid Sinus*

| Condition | Number of Cases | Age | Blood Pressure | | | Pulse Rate | | | Duration of BP and Pulse Rate Elevation, Min. |
|---|---|---|---|---|---|---|---|---|---|
| | | | Resting | Peak Level Following Block | Elevation Syst. Diast., Mm. | Resting | Peak Level | Elevation | |
| Normotension | 14 | 34 | 125/75 | 205/130 | 80/55 | 77 | 133 | 56 | 50 |
| Essential hypertension | 9 | 69 | 192/102 | 274/147 | 82/45 | 73 | 124 | 51 | 50 |
| Malignant hypertension | 6 | 45 | 220/134 | 321/187 | 101/53 | 86 | 136 | 50 | 45 |
| Chronic nephritis (hypertensive form) | 4 | 37 | 200/122 | 282/165 | 82/43 | 76 | 136 | 60 | 55 |

in that those for the hypertensive patients remain at a peak level for about 20 minutes before there is any decline.

In addition to blood pressure and pulse rate, the circulatory mechanism of neurogenic hypertension in man was examined. Using the physical analytic method of circulation (calculated from pulse wave velocity) described by Wezler and Böger,[7] the elastic and peripheral resistance and the cardiac output were established. The difficulties of accurate registration of the pulse delay and of calculation of the elasticity modulus are shown by the variable results found by different investigators. The results obtained with this method are, therefore, not considered to be absolute in their values. However, the relative shifting of the different circulatory factors following procaine block of the carotid sinus nevertheless gives a glimpse into the circulatory mechanism of neurogenic hypertension. In neurogenic hypertension at the peak level of response to procaine block a high cardiac output and a high minute volume were found. The peripheral resistance was at first unchanged and rose above the original level when the minute volume began to drop. The elasticity modulus of the large vessels, however, was elevated from the beginning and paralleled the minute volume. The same mechanism has been described by Lampen[8] in spontaneous neurogenic hypertension in polyneuritis involving and blocking the

6. Lampen, H.; Kezdi, P.; Koppermann, E., and Kaufman, L.: Experimenteller Entzügelungshockdruck bei arterieller Hypertonie, Ztschr. Kreislaufforsch. **38**:577-592, 1949.

7. Wezler, K., and Böger, A.: Die Dynamik des arteriellen Systems: Der arterielle Blutdruck und seine Komponenten, Ergebn. Physiol. **41**:292-606, 1939.

8. Lampen, H.: Über Entzügelungschockdruck bei Polyneuritis, Deutsche med. Wchnschr. **74**:536-540, 1949.

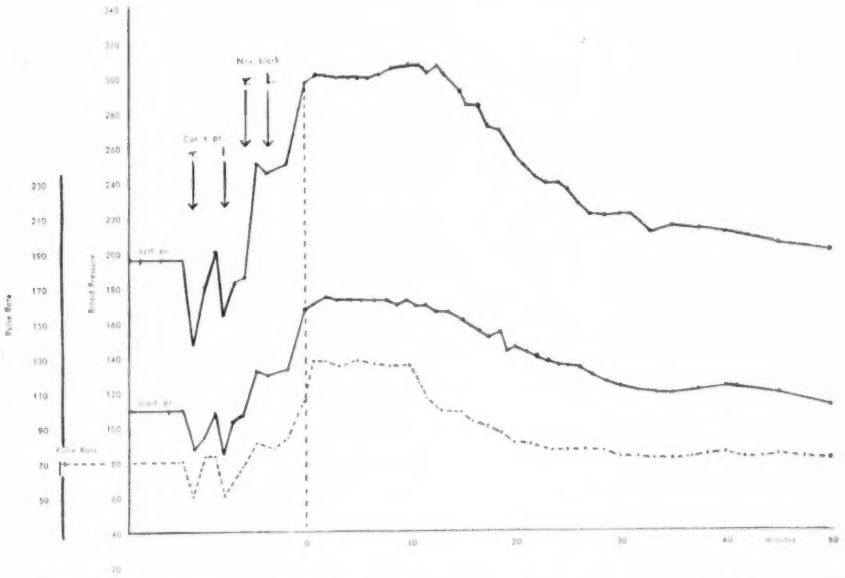

Fig. 2.—Graph showing results of procaine block of carotid sinus in patient with essential hypertension. Abbreviations are explained in legend to Figure 1.

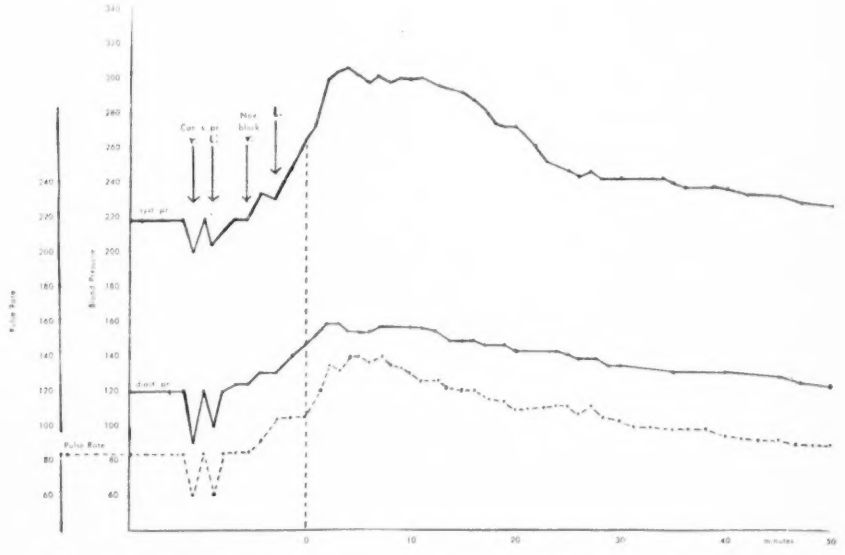

Fig. 3.—Graph showing results of procaine block of carotid sinus in patient with malignant hypertension. Abbreviations are explained in legend to Figure 1.

glossopharyngeal and carotid sinus nerves. In essential hypertension the cardiac output and the minute volume were normal or even lessened, while the elastic and the peripheral resistance were continuously high. In essential hypertension in which the carotid sinus is blocked, in addition to the circulatory mechanism of essential hypertension, an elevation of the minute volume and further elevation of the elastic and peripheral resistance resulted. This indicates that the blood pressure and pulse rate elevation in essential hypertension following carotid sinus block has the same mechanism as in neurogenic hypertension. An example of the changes in the different circulatory factors is given in Table 2.

### MECHANISM OF CAROTID SINUS SYSTEM

Comparison of results in normal and hypertensive patients shows no significant difference in the degree of blood pressure and pulse rate elevation; the hyper-

TABLE 2.—*Cardiac Output, Minute Volume, Elastic and Peripheral Resistance (Examined by Pulse-Wave-Delay-Measuring Method of Wezler and Böger) Before and After Bilateral Procaine Block of Carotid Sinus in a Normotensive Compared with Those in an Essential Hypertensive and a Malignant Hypertensive Patient*

| Time, Min. After Procaine Block | Blood Pressure | Pulse Rate | Pulse Wave Velocity, M./Sec. | Cardiac Output, C.c. | Minute Volume, Liters | Elasticity Modulus * | Peripheral Resistance † |
|---|---|---|---|---|---|---|---|
| **Normotensive Patient** | | | | | | | |
| Resting | 120/74 | 81 | 6.78 | 58.9 | 4,800 | 2,080 | 1,550 |
| 3 | 184/110 | 104 | 8.75 | 82.9 | 8,600 | 2,380 | 1,320 |
| 10 | 176/104 | 98 | 8.92 | 77.7 | 7,680 | 2,470 | 1,410 |
| 23 | 126/80 | 83 | 6.7 | 55.0 | 4,560 | 2,040 | 1,780 |
| **Essential Hypertensive Patient** | | | | | | | |
| Resting | 195/110 | 72 | 14.5 | 65.4 | 4,700 | 3,470 | 2,450 |
| 10 | 302/170 | 122 | 17.0 | 75.0 | 9,200 | 4,660 | 1,970 |
| 18 | 268/152 | 86 | 18.1 | 65.5 | 5,680 | 4,700 | 2,840 |
| 27 | 222/126 | 75 | 16.8 | 56.0 | 4,240 | 4,580 | 3,150 |
| **Malignant Hypertensive Patient** | | | | | | | |
| Resting | 200/135 | 92 | 12.2 | 44.5 | 4,100 | 3,900 | 3,180 |
| 5 | 320/180 | 150 | 17.7 | 59.8 | 8,550 | 6,950 | 2,250 |
| 18 | 310/170 | 150 | 15.0 | 64.2 | 9,620 | 5,810 | 1,910 |
| 26 | 238/165 | 130 | 14.4 | 39.0 | 5,100 | 5,000 | 3,960 |

* E = dyne/cm.$^2$
† W = dyne sec./cm.$^5$

tensive patients merely started at a higher level. If the carotid nerves were disrupted or their action diminished in these hypertensive persons, the addition of procaine block should not produce the same effect as it does in normotensive patients. Since the effect produced was the same, the conclusion is that the receptors of the carotid sinus nerves are not intrinsically affected in essential and malignant hypertension.

With this evidence the question arises: How can the carotid sinus have the same reaction to procaine block in normal and in hypertensive patients when the starting level of the blood pressure is so different? Is there no disturbance at all in the function of the sinoaortic regulatory system in hypertension? To determine this, we turned to the problem of the mechanism of stimulation of the carotid and aortic nerve receptors. Two principal theories have been advanced: 1. Intra-arterial pressure acting on the arterial wall compresses the receptors and thus stimulates them. 2. The pulsatile expansion of the walls of the aortic and carotid arteries stimulates the receptors. I believe the question has been settled by the

investigations of Hauss, Kreuziger, and Asteroth,[9] who studied a Heymans isolated carotid sinus preparation in dogs. They showed that no drop in blood pressure was seen in the femoral artery of the dog after elevation of the intra-arterial pressure in the isolated carotid artery if the arterial wall was surrounded by a rigid gypsum or lead cast or wrapped with silk. Before application of the cast or the silk and after its removal, the well-known depressor reflex occurred. This proves that the stimulus to the receptors of the blood pressure regulatory system is not intra-arterial pressure acting on the wall but expansion or stretching of the arterial wall. The pulsatile expansion of an arterial wall depends on its elasticity. Therefore the extent of the stimulation to the carotid sinus depends on the elasticity of the carotid arterial wall.

At this point one might review the physiology of the carotid sinus system. Measurement of the electrical discharge from the carotid sinus nerve reveals that each systolic pulse wave results in stimulation of the nerve. As the blood pressure rises, the stimulation is increased. Normal blood pressure is, therefore, envisioned as a balance between two forces, intrinsic vasomotor and cardiac accelerator tonus, on one hand, and repeated depressor action, on the other. The vasomotor or vasopressor tonus is determined by the vasomotor center and is actually set at a higher level than the normal but is constantly counteracted by the depressor reflex and thus results in the so-called normal blood pressure. The cardiac accelerator tonus operates similarly. When the action of the carotid and aortic nerves is removed, by either procaine block or section, the vasomotor and cardiac accelerator tonus rises to its uninhibited level, and hypertension and tachycardia develop.

A suspension of the carotid sinus reflex produces the same degree of elevation in blood pressure and pulse rate in hypertensive and in normotensive patients. The carotid sinus must, therefore, be under the same degree of stimulus in hypertension and in the normal state. This can be explained only by a loss of elasticity of the arterial wall in hypertension, necessitating a higher intra-arterial pressure to achieve the same pulsatile expansion of the wall and the same degree of stimulation as in normotension. The above-mentioned fundamental question—why hypertension is not reduced by the sinoaortic regulatory system—can be answered, therefore, as follows: The receptors of the carotid and aortic nerves perceive the elevated blood pressure in hypertension as being normal because the elevated blood pressure in hypertension causes the same degree of pulsatile expansion of the less elastic arterial walls and the same degree of stimulation to the carotid and aortic nerve receptors as the normal blood pressure in normotension. The carotid nerve is not disrupted; the defect is in the arterial wall. Thus, the sensitivity of the carotid sinus receptors is normal, and an apparently lessened sensitivity exists because of lessened elasticity of the arterial walls. The observation that in normotensive persons after procaine block an early decline and a secondary rise of the blood pressure curve occur which are absent in the hypertensive subject confirms this supposition. As the pharmacological effect of procaine is constant for about 30 minutes, some other factors must account for the initial decline in normotensive persons. In my opinion this counterregulatory effect comes from the aortic nerve, which was not blocked. In hypertensive persons

9. Hauss, W. H.; Kreuziger, H., and Asteroth, H.: Über die Reizung der Pressorezeptoren im Sinus caroticus beim Hund, Ztschr. Kreislaufforsch. **38**:28-33, 1949.

the persistent high blood pressure at the peak level is attributed to a lack of counterregulation from the aortic nerve. This lack of counterregulation is probably due to the failure of stimulation of the aortic nerve receptors because of loss of elasticity of the aorta.

The normal histological picture of the wall of the carotid artery in the region of the carotid bulb differs from the usual picture of the large arteries. It shows a decrease in the muscle layer of the media, with replacement by elastic fibers and a thickened adventitia. The receptors of the carotid nerves involve the entire adventitia up to the media. This special histological structure, which was described by de Castro,[10] refers to the important function of the carotid bulb as an elastic organ. This elastic histological structure is comparable with the structure of the initial part of the aorta and pulmonary artery. Studies on the elasticity of the aorta have been performed by Katz and co-workers.[11] Hallock and Bensen[12] examined the elasticity of human aortas. They found a decreased elasticity in specimens from older age groups. The elasticity of the carotid artery in man has been studied by Asteroth and Kreuziger.[13] These studies showed a definite loss of the elasticity in hypertensive persons as compared with normotensive persons of the same age group. These observations tend to confirm the above-explained mechanism of the carotid sinus in hypertension.

## PATHOGENESIS OF HYPERTENSION

These results in hypertensive research led Volhard[14] to develop his theory of the pathogensis of essential and malignant hypertension:

In some persons there is a hereditary predisposition toward degenerative processes of the arterial walls. These degenerative processes can develop, under influence of hormonal and metabolic factors, at any age but are commonest in the second half of life. Nervous tension and exercise tend to elevate the blood pressure in any person. These excesses in blood pressure elevation, which are greater in labile psychoneurotic patients and are due to tachycardia and high minute volume, lead in those with hereditary predisposition to degeneration of the elastic fibers of the carotid artery and aortic wall and to diminution of their elasticity. The pulsatile expansion is lessened, and the sinoaortic regulatory system is understimulated. The balance is thus shifted to a higher level of pressure as the result of vasoconstriction in the periphery, until the intra-arterial pressure is high enough to give full stimulation of the receptors. However, nervous tension and other factors continue to act, and the elasticity is again lessened. The whole system again moves upward until stimulation of the regulatory system is adequate to achieve a balance. A

10. de Castro, F., in Ergebnisse der Kreislaufforschung, edited by B. Kisch, Vol. 1, Koch, E.: Die reflektorische Selbststeuerung des Kreislaufes, Dresden, Theodore Steinkopff, 1931.

11. Katz, L. N.; Malinow, M. R.; Kanto, B.; Feldman, D., and Grossmann, N.: Volume Elasticity of Aorta in Intact Dog, Am. Heart J. **33**:319-331, 1947.

12. Hallock, P., and Benson, I. C.: Studies on Elastic Properties of Human Isolated Aorta, J. Clin. Invest. **16**:595-602, 1937.

13. Asteroth, H., and Kreuziger, H.: Dehnungsstudien am isolierten Sinus caroticus von verstorbenen Normotonikern und Hypertonikern, Ztsch. Kreislaufforsch. **40**:11-15, 1951.

14. Volhard, F.: Hochdruck: Klinisches Referat, in Verhandlungen der deutschen Gesellschaft für Kreislaufforschung, Frankfurt am Main, Theodore Steinkopff, 1949, pp. 15-40; Über die Pathogenese des roten (essentiellen) arteriellen Hochdrucks und der malignen Sklerose, Schweiz. med. Wchnschr. **78**:1189-1194, 1948.

further vasoconstriction raises the blood pressure, which leads to muscular hypertrophy of the constricted arterioles, later to arteriolar sclerosis and secondary sclerosis of the larger vessels, thus fixing the hypertension. At this level the regulation in the sinoaortic regulatory system is balanced because the elevated blood pressure is perceived as normal and tachycardia and high minute volume do not develop as they do in neurogenic hypertension. Thus, the vicious circle continues until the cardiocirculatory system fails, in the form of either decompensation or rupture of a vital vessel.

If the vasoconstriction involves the kidney arterioles during the development of essential hypertension, in addition to the sinoaortic mechanism, the renal mechanism begins to act, and malignant hypertension develops. Essential hypertension can thus become malignant in any age group. In earlier age groups there is a tendency toward muscular hypertrophy of the arterioles, especially of the kidney, as a result of the permanent vasocontriction. In later age groups the degenerative processes are already well established. Therefore, the earlier in life that hypertension begins, the greater the tendency for development of a renal mechanism superimposed upon the neurogenic. This would explain why a young person's hypertensive course is so often malignant. The essential stage can be short and not discovered. In these patients death can result from renal failure.

Lessened pulsatile expansion of the vessel system in older persons does not always lead to hypertension. If the loss of elasticity of the large vessels develops in persons of older age groups, it often goes along with a dilatation of the sclerotic aorta and of the initial part of the large arteries. It is known from the physical laws of circulation that in an enlarged vessel system the blood flow loses its velocity and in the more distal vessel system the lateral pressure is decreased. Thus, the elevated blood pressure expected in the presence of a decreased pulsatile expansion is compensated for by the dilatation of the aorta. Following the physical laws of circulation in the presence of a dilated aorta, the diastolic pressure should be even lower than is actually found. However, the understimulated sinoaortic regulatory system elevates the peripheral resistance because of vasoconstriction which counteracts the diastolic fall in blood pressure. Arteriosclerotic old persons consequently can have symptoms of vasoconstriction without hypertension.

The above-mentioned explanation further suggests that the vasoconstriction in essential hypertension is probably not humoral but is due to the vasopressor nerves, and that in malignant hypertension the humoral mechanism is secondarily superimposed upon the primary neurogenic mechanism. Unphysiologically high levels of vasopressor substances are required to produce experimental hypertension in normal persons, levels which have never been found in hypertensive patients except in acute nephritis by Dexter and Haynes.[15] If a pure humoral hypertension is produced by intravenous infusion of arterenol or renin, the depressor reflex is stimulated and bradycardia develops.[16] The blood pressure would be higher if

15. Dexter, L., and Haynes, F. W.: Relation of Renin to Human Hypertension with Particular Reference to Eclampsia, Preeclampsia, and Acute Glomerulonephritis, Proc. Soc. Exper. Biol. & Med. **55**:288-290, 1944.

16. Moeller, J., and Koppermann, E.: Kreislaufreaktionen auf Arterenolinfusionen bei Normotonikern und bei Hypertonikern, Ztschr. Kreislaufforsch. **39**:333-346, 1950. Koppermann, E.: Die Hämodynamischen Kreislaufreaktionen bei natürlicher und experimenteller renal-humoraler Hypertension, ibid. **39**:161-167, 1950.

the sinoaortic regulatory system did not counteract the elevation. In acute nephritis, if no cardiac insufficiency develops, there is characteristically a bradycardia which many authors believe is due to the depressor reflex working against the humoral hypertension. In chronic nephritis the pulse rate is normal. Procaine block of the carotid sinus in four patients with chronic nephritis (Table 1) showed the same effect as in those with essential and malignant hypertension.[17] The conclusion is that the carotid sinus nerves are not disrupted and that the regulatory mechanism works normally from the higher blood pressure level present in chronic nephritis. The primary humoral blood pressure elevation results after a certain time in a secondary loss of elasticity of the arterial walls; in addition to the humoral mechanism, the sinoaortic regulatory system is understimulated, which leads to further neurogenic vasoconstriction. This mechanism is the reverse of the mechanism of malignant hypertension. Malignant hypertension and chronic nephritis (especially the hypertensive form) are, therefore, often similar in their end-stages, and differential diagnosis is difficult, not only clinically but pathologically.

SUMMARY

Works on carotid sinus block in normotensive and hypertensive subjects are summarized, and two important conclusions are made:

1. The receptors of the carotid sinus nerves are not disrupted in essential and malignant hypertension, and their regulatory mechanism acts normally from the higher blood pressure level.

2. The extent of stimulation to the carotid sinus depends on the elasticity of the carotid arterial wall, and in hypertension this elasticity is lessened. The receptors of the carotid nerves perceive the elevated blood pressure in these hypertensions, therefore, as being normal because the elevated blood pressure in hypertension causes the same degree of pulsatile expansion of the less elastic arterial walls and the same degree of stimulation to the carotid sinus receptors as does the normal blood pressure in normotensive persons.

Some of the theories of hypertension are reviewed, and evidence for the role of the sinoaortic regulatory system in the pathogenesis of essential and malignant hypertension, based on results of procaine block of the carotid sinus, is presented.

Methodist Hospital.

17. Lampen, H.; Kezdi, P., and Kopperman, E.: Karotissinusblockade bei akuter und chronischer Nephritis, Ztschr. Kreislaufforsch. **38**:726-737, 1949.

# VARICELLA PNEUMONIA

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CHICKEN pox is usually a mild and benign disease. However, previous reports [1] have demonstrated that complications, although infrequent, may be of unusual severity. Primary varicella pneumonia has been reported so rarely that one may fail to anticipate the potential severe pulmonary manifestations which can occur. It is the purpose of this report to describe severe varicella pneumonia seen in three adults within a five-month period.

## REPORT OF CASES

CASE 1.—T. B., a 38-year-old white engineer, was admitted to the Ohio State University on Feb. 24, 1952, in acute respiratory distress. Five days prior to admission he noted mild malaise and a few "watery pimples" on his scalp. The following day there was marked involvement of his forehead, face, chest, and abdomen, with fewer lesions on the extremities. At this time he realized he had chicken pox, since there was a considerable amount of it in the community where he was working. He noted substernal pain on deep respiration and marked dyspnea three days before admission, at which time he consulted a local physician, who prescribed streptomycin and "fever pills." His symptoms became progressively worse and were accompanied by marked fever, anorexia, nausea, prostration, and cough productive of blood-tinged sputum. The patient had never had chicken pox before and had always been in excellent health. A review of systems was otherwise noncontributory.

Physical examination revealed a well-developed, well-nourished man who was critically ill. He was cyanotic, orthopneic, and markedly dyspneic. His skin showed characteristic varicella macules, papules, and vesicles over the scalp, face, chest, abdomen, extremities, palms, and soles.

From the Department of Medicine, Ohio State University College of Medicine.

1. (*a*) Bullowa, J. G. M., and Wishik, S. M.: Complications of Varicella; Their Occurrence Among 2,534 Patients, Am. J. Dis. Child. **49**:923-926, 1935. (*b*) Rausch, L. E.; Grable, T. J., and Musser, J. H.: Atypical Pneumonia Complicating Severe Varicella in Adult, New Orleans M. & S. J. **96**:271-275, 1943. (*c*) Waring, J. J.; Neubuerger, K. T., and Geever, E. F.: Severe Forms of Chickenpox in Adults, with Autopsy Observations in Case with Associated Pneumonia and Encephalitis, Arch. Int. Med. **69**:384-408, 1942. (*d*) Grayson, C. E., and Bradley, E. J.: Disseminated Chickenpox (Pneumonia and Nephritis), J. A. M. A. **134**:1237-1239, 1947. (*e*) Wesselhoeft, C., and Pearson, C. M.: Orchitis in the Course of Severe Chicken Pox with Pneumonitis, Followed by Testicular Atrophy, New England J. Med. **242**:651-652, 1950. (*f*) Claudy, W. D.: Pneumonia Associated with Varicella, Arch. Int. Med. **80**:185-192, 1947. (*g*) Michel, J. C.; Coleman, D. H., and Kirby, W. M. M.: Pneumonia Associated with Chickenpox: Report of a Patient Treated with Aureomycin, Am. Pract. & Digest. Treat. **2**:57-59, 1951. (*h*) Frank, L.: Varicella Pneumonitis: Report of Case with Autopsy Observations, Arch. Path. **50**:450-456, 1950.

The temperature was 104 F. (rectally), pulse rate 130, and respirations 30 and shallow. Examination of the chest revealed no dullness to percussion, and only a few fine crepitant rales were heard in both bases posteriorly. All other physical findings were within normal limits.

Laboratory studies at this time showed a total white cell count of 11,850, with 55% neutrophiles, 35% lymphocytes, 4% monocytes, and 2% eosinophiles. Routine urine examination gave results within normal limits. Repeated sputum examinations showed predominantly Neisseria

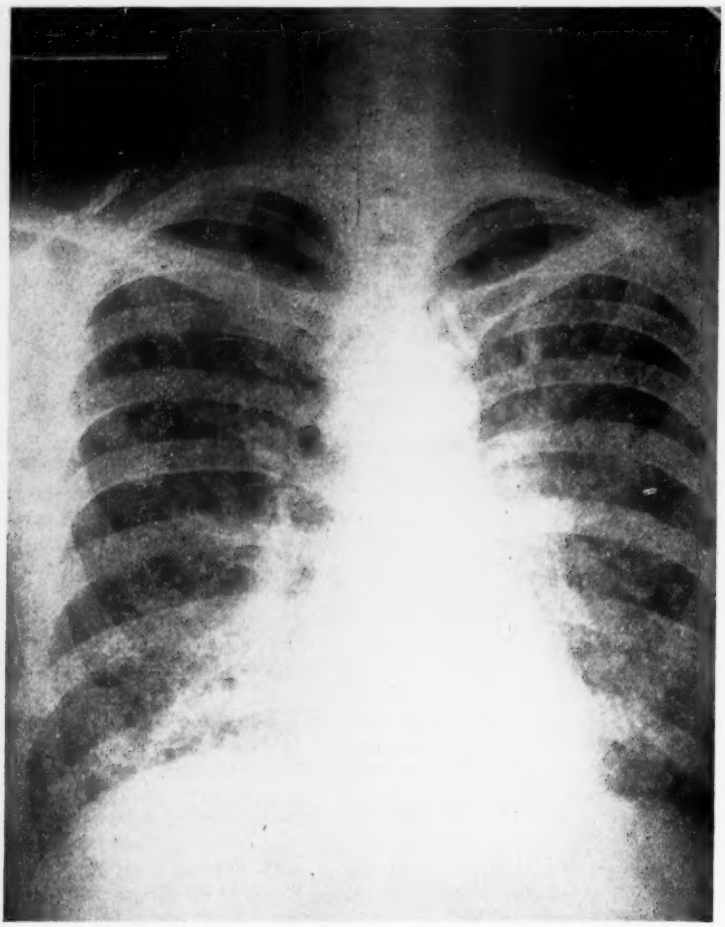

Fig. 1 (Case 1).—Roentgenogram taken with a portable machine Feb. 26, 1952, showing extensive bilateral nodular infiltration and hilar adenopathy.

catarrhalis and alpha streptococci but no pneumococci, hemolytic streptoccci, or other potentially pathogenic bacteria. Blood cultures were negative. An x-ray taken on admission with a portable machine showed an extensive diffuse mottled miliary process throughout both lungs (Fig. 1). Serial cold agglutinations and serologic studies for psittacosis and Q fever were negative.

*Hospital Course.*—Immediately upon admission the patient was placed in an oxygen tent, prophylactic administration of penicillin was begun, and 2,000 cc. of 10% glucose in water

was given intravenously. After two days his temperature returned to normal and he appeared considerably improved. His cough improved gradually, but his sputum contained small crusts that closely resembled the skin crusts. With the clearing of the skin lesions there was a concomitant improvement in the chest roentgenograms. One week after admission chest x-ray revealed marked clearing of the lung fields characteristic of a resolving pneumonia (Fig. 2). The patient was discharged on the 14th hospital day. Six weeks after discharge a chest x-ray taken in Detroit showed some residual basilar infiltration (Fig. 3).

CASE 2.—B. S., a 42-year-old white man, a painter, was admitted to University Hospital in acute respiratory distress on March 22, 1952. About 19 days before admission he had been

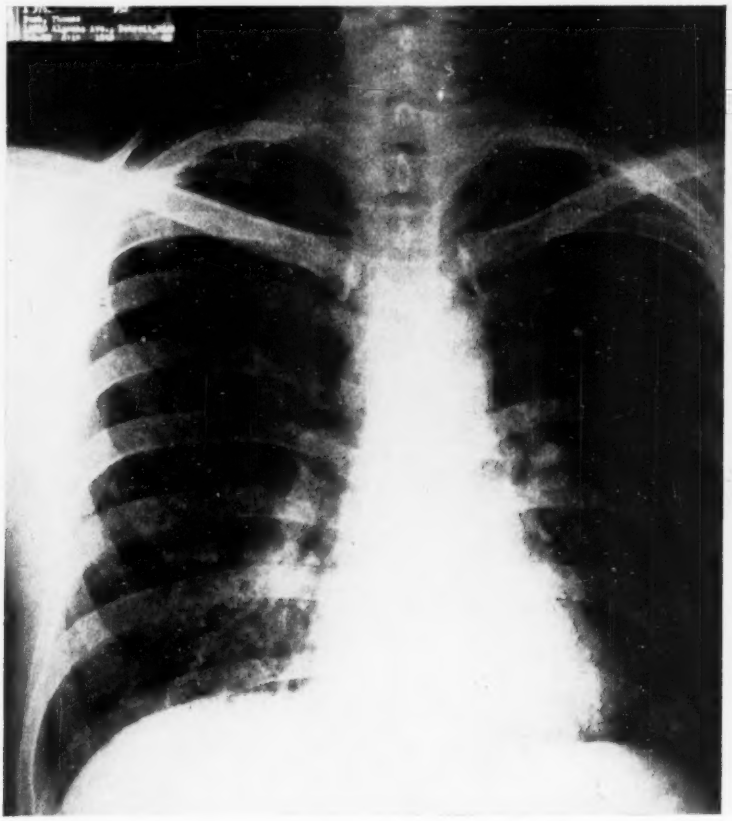

Fig. 2 (Case 1).—Chest roentgenogram taken March 4 revealing marked resolution of nodular infiltration of both lungs.

exposed to chicken pox in a home where he was doing interior decorating. On March 12 he noted generalized malaise and aching, which persisted until March 16, when an eruption appeared on his face, neck, and chest and in his mouth. By the following day his entire body was involved, including the palms and soles. By March 20 he had a cough productive of blood-tinged sputum and marked fever, both of which became worse, necessitating his admission to the hospital. He had never had chicken pox. His past history was otherwise noncontributory.

Physical examination revealed a well-developed, well-nourished white man appearing moderately dyspneic and coughing frequently. The temperature was 103.8 F. (rectally), pulse rate 108, respirations 36, and blood pressure 128/88. The skin and mucous membranes of the mouth

were covered with numerous macules, papules, and vesicles characteristic of varicella. His lungs were clear to percussion and auscultation. The rest of the physical examination was essentially negative.

Laboratory studies at this time showed a total white cell count of 13,400, with 69% neutrophiles, 29% lymphocytes, 1% monocytes, and 1% eosinophiles. The red cell count was 4,970,000, with 14.4 gm. of hemoglobin. Urinalysis gave results within normal limits. Repeated sputum examinations showed no significant pathogenic bacteria. A second blood study two days later revealed a total white cell count of 6,000, with a normal differential count. An x-ray of the chest taken on admission showed a diffuse nodular miliary infiltration in all lung fields (Fig. 4). Serial cold agglutinations and serologic studies for psittacosis and Q fever were negative.

Fig. 3 (Case 1).—Chest roentgenogram taken April 25 shows further clearing, but some residual infiltration remains in both bases.

*Hospital Course.*—The patient was placed in an oxygen tent and was given 500 mg. of aureomycin every six hours. He showed a gradual improvement and was afebrile and feeling well by the third hospital day. Concomitant with the clearing of his skin there was resolution of the lung fields. The patient was discharged on the 14th hospital day, at which time his chest x-ray showed no evidence of the previous diffuse inflammatory reaction except for minimally prominent hilar shadows (Fig. 5).

CASE 3.—M. O'N., a 28-year-old white housewife, was admitted to University Hospital on July 25, 1952, in acute respiratory distress. She had been exposed to chicken pox for a month, during which time her three children had the disease. On July 20 she noted fever, malaise, and aching and observed numerous skin lesions on her face and neck, which spread the following

day to her entire body. She attempted to continue her housework but became progressively anorexic and dyspneic. She did not respond to penicillin therapy at home and consequently was referred to the hospital.

The past history was noncontributory.

Physical examination revealed an acutely ill, prostrated, stuporous, and dyspneic woman with moderate cyanosis. The temperature was 102 F. (rectally), pulse rate 110, respirations 40, and

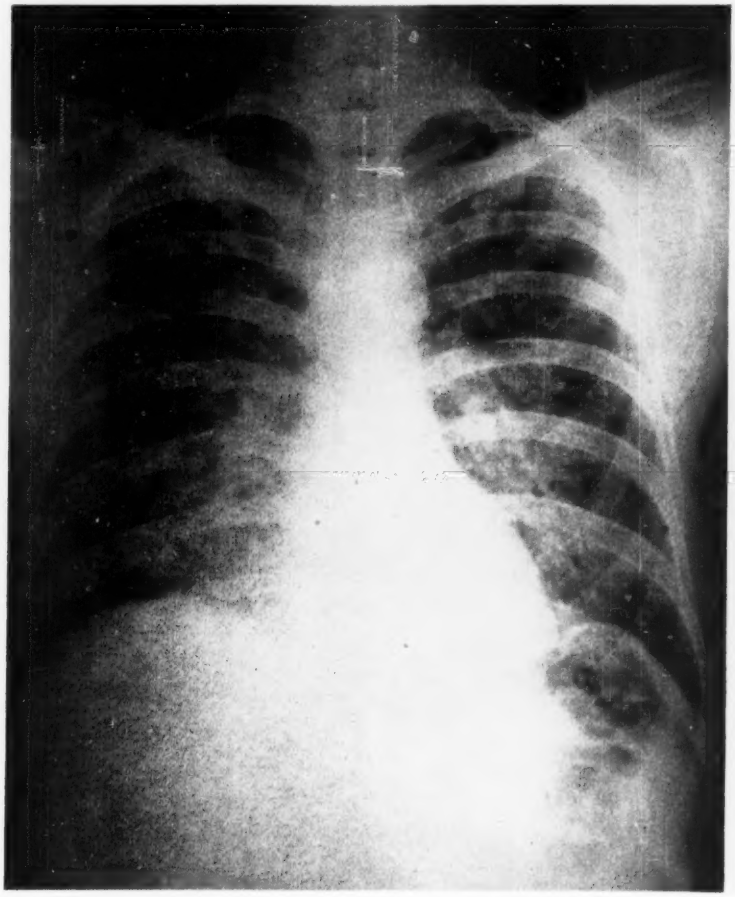

Fig. 4 (Case 2).—Chest roentgenogram taken on admission (March 22, 1952), showing extensive nodular infiltration throughout both lungs and swelling of both hili.

blood pressure 118/70. Her entire skin was covered densely with macules, papules, and vesicles. Examination of the chest revealed fine rales and rhonchi in the bases. The rest of the examination was negative.

Admission laboratory studies showed a total white cell count of 4,300 with 74% neutrophiles, 34% lymphocytes, 1% monocytes, and 1% eosinophiles. The sputum was blood-tinged but did not contain any potentially pathogenic organisms. Serial serologic studies for primary atypical pneumonia, psittacosis, and Q fever were negative. A chest roentgenogram revealed a marked nodular infiltration in both lungs sparing only the extreme apices and bases (Fig. 6).

*Hospital Course.*—The patient was placed immediately in an oxygen tent, administration of penicillin was begun, and she was given an infusion of 10% dextrose in water. She showed gradual improvement and was afebrile and alert by the third hospital day. However, on the fifth hospital day it was noted that phlebothrombosis had developed in both legs. Despite anticoagulant therapy she experienced a right lower lobe pulmonary embolus four days later. The rest of her hospital stay was primarily for this ailment, and she was discharged on the 18th hospital day fully recovered. X-rays taken at this time showed clearing of the pulmonary infiltrations, although evidence of the pulmonary infarct was seen in the right lower lobe (Fig. 7).

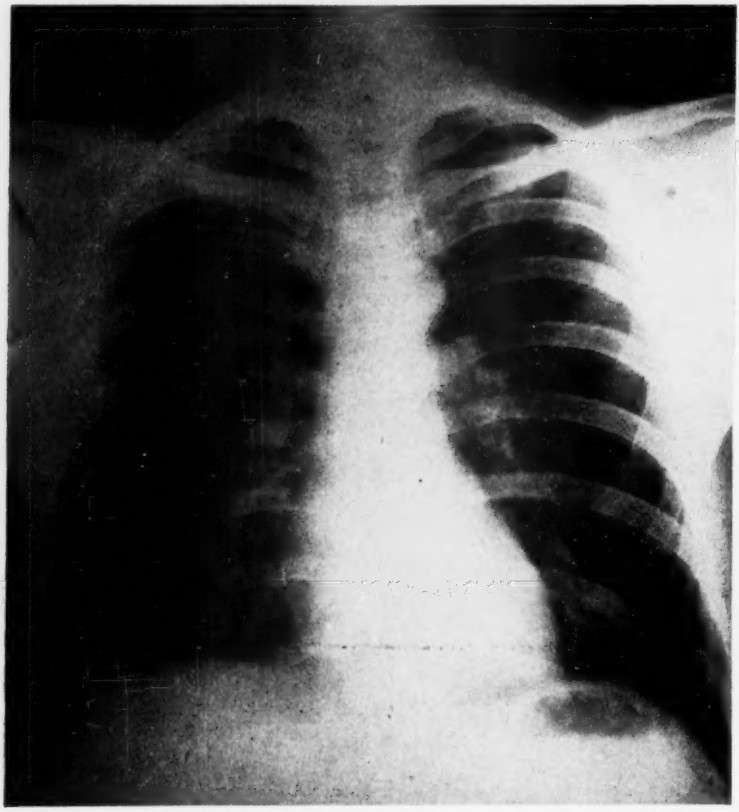

Fig. 5 (Case 2).—Chest roentgenogram taken April 4 reveals complete clearing of the diffuse inflammatory reaction, although moderate enlargement of hilar structures persists.

## COMMENT

Varicella pneumonia has been described on relatively few occasions. Bullowa and Wishik [1a] reported 21 cases of pneumonia among 2,534 hospital cases of chicken pox. However, details on the character of the pneumonia are lacking, and the recovery of hemolytic streptococci from the patients would suggest that their disease may have been secondary bacterial pneumonia. Thus, to our knowledge only eight cases have been reported in which the varicella virus appeared to be the causative agent of the pneumonitis. Rausch, Grable, and Musser [1b] cited one case, with

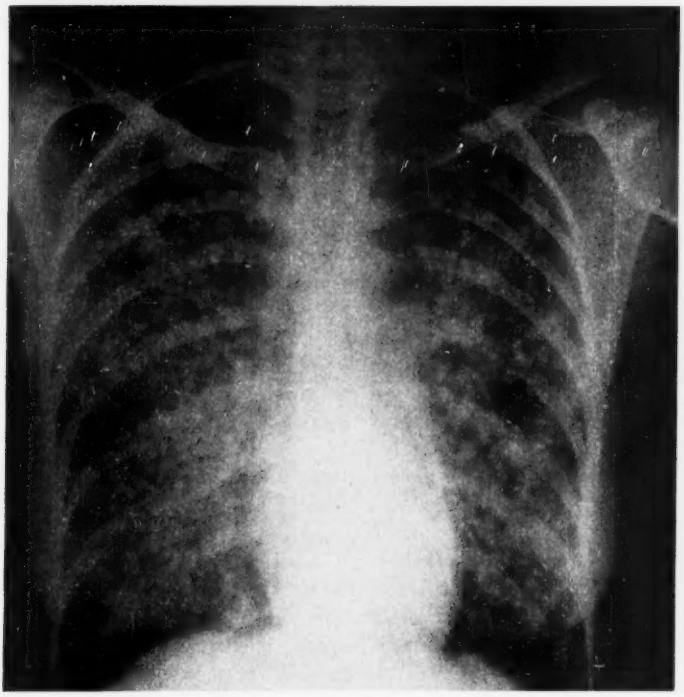

Fig. 6 (Case 3).—Chest roentgenogram taken July 25, 1952, showing extensive nodular infiltration in both lungs.

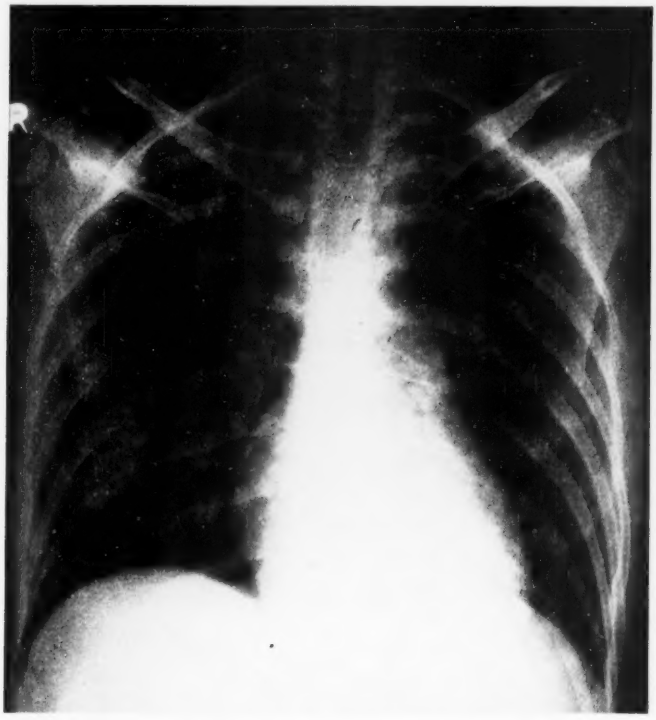

Fig. 7 (Case 3).—Chest roentgenogram taken 12 days after admission shows resolution of diffuse infiltration. A roughly triangular area of infiltration is seen in the right lower lobe as the result of the pulmonary infarction.

recovery, in a 27-year-old white man, and Waring, Neubuerger, and Geever [1c] reported on two white men, 33 and 40 years of age, of whom the latter died. Grayson and Bradley [1d] described a similar case in a 34-year-old white man, with recovery. Wesselhoeft and Pearson [1e] noted both orchitis and miliary pneumonia in a 46-year-old white man, while Claudy [1f] and Frank [1h] reported fatal varicella pneumonia in a 32- and a 34-year-old white woman, respectively. Michel, Coleman, and Kirby [1g] described widespread bilateral pulmonary infiltration in a 27-year-old white woman, with a rapid recovery.

The admission to University Hospital within a short period of three patients with varicella and associated pneumonitis presented us with an unusual opportunity to study this disease. It is of interest that three patients were adults aged 28, 38, and 42. All three showed rapid improvement in their clinical condition. The nodular pulmonary infiltrates were markedly similar. The pneumonia in the three patients was in all probability caused by the varicella virus. The paucity of findings in the lungs on physical examination was in distinct contrast to the extensive infiltration seen in the chest roentgenograms. The clearing of the lung fields paralleled the improvement of the skin lesions, although in patient T. B. some residual infiltration was present in the lower lobes two months after the onset of the varicella pneumonia. Blood cultures were negative in all instances. Results of sputum examinations were not consistent with those observed in bacterial pneumonia. Leucocyte counts were only moderately elevated in two patients and not increased in the third. Serial serologic studies, although not conclusive evidence, were negative for primary atypical pneumonia, psittacosis, and Q fever. The marked similarity in the epidemiologic, clinical, and roentgenologic aspects in all three patients was striking.

Postmortem studies of fatal adult [2] and congenital chicken pox [3] have demonstrated that the virus can involve the lungs as well as other viscera.

The dramatic recovery of all three patients was not attributed to any specific action of antibiotics on the varicella virus. The penicillin used in two cases and the aureomycin in the third may have prevented secondary bacterial complications. The treatment was primarily supportive during the first few days of critical illness, after which the pulmonary distress was greatly ameliorated.

## SUMMARY

A severe virus type of pneumonia with extensive bilateral nodular pulmonary infiltrates was observed in three adults with chicken pox. The parallel clearing of both lungs and skin indicate a common etiology. Additional evidence is presented that a usually benign disease like chicken pox may on occasion cause severe pulmonary disease, particularly in adults.

2. Eisenbud, M.: Chicken Pox with Visceral Involvement, Am. J. Med. **12**:740-746, 1950. Waring, Neubuerger, and Geever.[1c] Claudy.[1f] Frank.[1h]

3. Oppenheimer, E. H.: Congenital Chickenpox with Disseminated Visceral Lesions, Bull. Johns Hopkins Hosp. **74**:240-250, 1944. Johnson, H. N.: Visceral Lesions Associated with Varicella, Arch. Path. **30**:292-307, 1940. Lucchesi, P. F.; LaBoccetta, A. C., and Peale, A. R.: Varicella Neonatorum, Am. J. Dis. Child. **73**:44-54, 1947.

# BONE MARROW DEPRESSION FROM CHLORAMPHENICOL

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IN RECENT months several reports have appeared incriminating chloramphenicol as an etiological agent in bone marrow depression.[1] Most of these reports have described patients with an established anemia and hypoplastic marrow who gave a history of having received varying amounts of chloramphenicol.[2] A few have described patients in whom neutropenia developed during a course of the antibiotic.[3] The present article reports serial observations on a patient who, while undergoing hematological study for other purposes, showed evidence of depression of erythropoiesis and of granulopoiesis during an episode of treatment with chloramphenicol.

## REPORT OF CASE

*History.*—A 51-year-old white man, an electrician, was admitted on Feb. 11, 1952, to the James Ewing Hospital with a complaint of anemia of four years' duration.

Four years before admission he consulted his local physician for a check-up, although he felt entirely well and had not sought medical consultation for the preceding 20 years. His local physician found his hemoglobin to be "65%," and the patient then received liver injections weekly and took iron orally each day for 18 weeks. There was no improvement with this regimen, and the patient then stopped treatment of his own accord and continued to work.

Three years before admission he began to notice loss of stamina, fatigue, headaches, dyspnea, and palpitations on slight exertion. After a few months of progressive symptoms he consulted another physician, who found his hemoglobin level to be "42%." The patient received liver injections for the next two weeks. There was no improvement, and he was then admitted to another hospital, where a diagnosis of pernicious anemia was made. He was given three transfusions and then discharged, slightly improved.

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1. (*a*) Volini, I. F.; Greenspan, I.; Ehrlich, L.; Gunner, J. A.; Felsenfeld, O., and Schwartz, S. O.: Hemopoietic Changes During Administration of Chloramphenicol (Chloromycetin®), J. A. M. A. **142**:1333, 1950. (*b*) Gill, P. F.: Agranulocytopenia Following "Chloromycetin": A Report on 2 Cases, M. J. Australia **1**:768, 1950. (*c*) Rich, M. L.; Ritterhoff, R. J., and Hoffman, R. J.: A Fatal Case of Aplastic Anemia Following Chloramphenicol (Chloromycetin) Therapy, Ann. Int. Med. **33**:1459, 1950. (*d*) Claudon, D. B., and Holbrook, A. A.: Fatal Aplastic Anemia Associated with Chloramphenicol (Chloromycetin®) Therapy, J. A. M. A. **149**:912, 1952. (*e*) Smiley, R. K.; Cartwright, G. E., and Wintrobe, M. M.: Fatal Aplastic Anemia Following Chloramphenicol (Chloromycetin®) Administration, ibid. **149**:914, 1952. (*f*) Sturgeon, P.: Fatal Aplastic Anemia in Children Following Chloramphenicol (Chloromycetin®) Therapy, ibid. **149**:918, 1952. (*g*) Lindan, W.: Effect of Chloromycetin upon Erythropoiesis, read at the Proceedings of the American Federation for Clinical Research, Atlantic City, N. J., May 4, 1952.

2. Rich, Ritterhoff, and Hoffman.[1c] Claudon and Holbrook.[1d] Smiley, Cartwright, and Wintrobe.[1e] Sturgeon.[1f]

3. Volini and associates.[1a] Gill.[1b]

For the next year he received weekly intramuscular injections of liver extract and took three tablets a day of folic acid and of iron. There was no improvement with this regimen.

Two years before admission he was treated by another local physician, who gave him intramuscularly 30 units a day of liver extract plus 15 γ a day of vitamin $B_{12}$ for two weeks. Since there was no response to this therapy, he received repeated transfusions, from which he obtained only temporary symptomatic relief.

One year before admission he was admitted to the New York Hospital, where investigation showed the presence of free gastric hydrochloric acid, serum bilirubin at the upper limit of normal, an increased fecal urobilinogen, and an erythroblastic marrow. No diagnosis was made and no therapy given. The patient was repeatedly given transfusions and observed at regular intervals in the outpatient department. Except for the consequences of transfusion there was no significant change in his condition.

Four months before admission he was readmitted to the New York Hospital for reevaluation. At that time his hematological values were as follows: hemoglobin 6.7 gm. per 100 cc.; hematocrit reading 21.0%; red cells 2,070,000 per cubic millimeter, and white blood cells 6,100 per cubic millimeter, with 42% polymorphonuclears, 12% band cells, 35% lymphocytes, 1% eosinophiles, 5% basophiles, and 5% monocytes. The mean corpuscular volume was 101 cubic microns; the mean corpuscular hemoglobin concentration, 32%, and the mean corpuscular hemoglobin, 32 micromicrograms. The reticulocyte count was 1.8%. On smear the red blood cells were macrocytic and showed marked variation in size and shape. There were no multilobed polymorphonuclear cells. The platelets appeared abundant on smear. The Coombs test was negative. The bone marrow again appeared erythroblastic. The patient, of blood type B, Rh positive, was given a transfusion containing 3 units of sedimented normal type O, Rh-positive cells, and the survival of the transfused cells was followed by differential agglutination and found to be normal (115 days). Toward the end of the survival study the patient was admitted to the James Ewing Hospital for further study.

It should be noted that during his entire illness the patient never had anorexia or other gastrointestinal symptoms. There was no dietary irregularity. Loss of stamina, fatigue, dyspnea, and palpitations were noted only when his hemoglobin fell below 50%. During the year before admission he occasionally noted paresthesias of the hands and feet, but again only when his hemoglobin fell below 50%; these symptoms were completely relieved by transfusion.

He was employed for more than 20 years before admission by a public utility company as an electrician and maintenance supervisor. There was no known exposure to benzene or other industrial intoxicants, to radiation, or to any medication other than acetylsalicylic acid and cascara. There was no history of allergic manifestations.

*Physical Examination.*—On examination the patient was seen to be a large-framed, middle-aged white man who appeared pale. His hair was gray, his complexion fair. He displayed no acute distress, but he did appear worn and tired. There was no jaundice. There were no hemorrhagic manifestations. The tongue was not atrophic or reddened. There was no lymphadenopathy. The chest was clear to percussion and auscultation. The heart was not enlarged; the rhythm was normal; the sounds were of good quality, and there were no murmurs. The abdomen was muscular; the liver edge could be felt 6 to 8 cm. below the costal margin in the midclavicular line; the spleen could not be felt. Rectal examination revealed a slightly enlarged prostate, which was symmetrical and of normal consistency. There was a slight edema of the feet. The neurological examination was entirely normal.

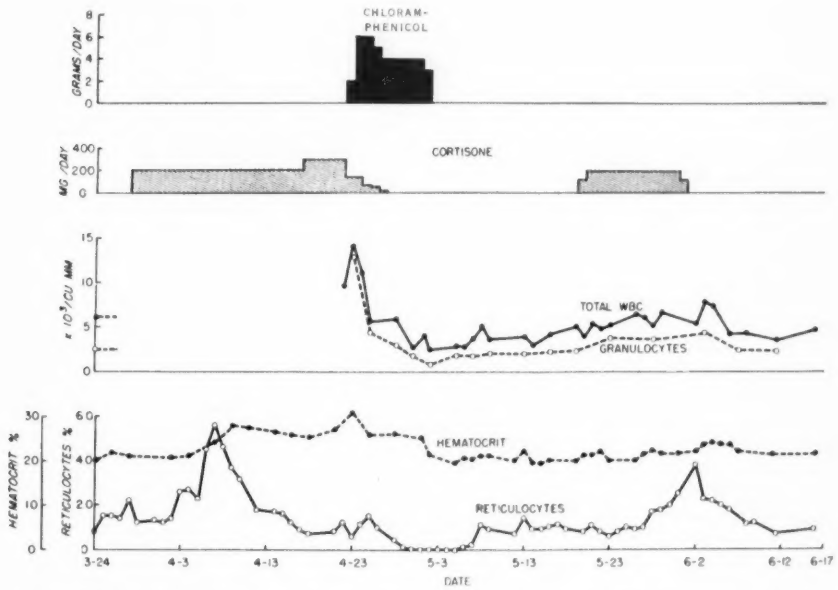
*Laboratory Examinations.*—Hemoglobin was 7.4 gm. per 100 cc., hematocrit reading 22%, red cell count 1,960,000 per cubic millimeter, mean corpuscular volume 117 cubic microns, mean corpuscular hemoglobin concentration 34%, and mean corpuscular hemoglobin 38 micromicrograms. The reticulocyte count was 2.1%. Examination of a stained smear showed macrocytic red blood cells with marked variation in size and shape. The red cells strongly resembled those seen in pernicious anemia. The white cells, however, did not appear abnormal, and the platelets appeared abundant and morphologically normal. A bone marrow aspiration from the iliac crest revealed hyperplasia with a marked increase in erythroblasts and normoblasts. There were no abnormal forms among the red cell precursors, and the granulocytic series appeared normal. Megakaryocytes were present in normal numbers and forms.

Urinalysis showed a specific gravity varying on casual specimens from 1.010 to 1.026. Occasional very faint traces of albumin and rare white blood cells in the centrifuged sediment were noted.

The serum bilirubin varied from 0.28 to 0.90 mg. per 100 ml. The total serum protein was 7.0 gm. per 100 ml., with 4.25 gm. of albumin and (by difference) 2.75 gm. of globulin. The serum alkaline phosphatase was 3.8 units, the serum cholesterol 110 mg., and the blood uric acid 4.65 mg. per 100 ml. The thymol turbidity was 1.04 units (normal up to 1.86). The retention of sulfobromophthalein (bromsulphalein®) was 7%.

The basal metabolic rate was —1%.

Stools showed an occasional slightly positive guaiac test; but when the patient was temporarily placed on a meat-free diet, the stool guaiac test was consistently negative. No ova or parasites were seen.




Blood values during cortisone therapy and during administration of chloramphenicol for cellulitis of the orbit.

A urobilinogen determination on a four-day stool collection yielded an output of 236 mg. of fecal urobilinogen a day. In relation to a hemoglobin of about 7.0 gm. per 100 cc., this is a significantly elevated value.

X-ray examination of the chest and electrocardiographic findings were within normal limits.

*Course.*—During the initial month after admission, while the laboratory data were being collected and a radioiron utilization study was being conducted (with a tracer dose of $Fe^{55}$), the patient received no therapy. His hemoglobin varied between 6.6 and 7.9 gm. per 100 cc., his hematocrit reading from 20.0 to 24.0%, his red cell count from 1,850,000 to 2,320,000 per cubic millimeter, and his reticulocyte count from 0.4 to 2.3%. His white cell count was not followed.

On the 31st hospital day a 10-day course of treatment was begun with crude liver extract (Lilly), 12 gm. a day being given orally. There was no reticulocyte or other response.

On the 44th hospital day the patient began to receive cortisone in a dose of 200 mg. a day by mouth. On the 55th day the reticulocyte count reached a peak of 5.8%. The use of

cortisone was continued, and, although the reticulocyte count gradually subsided to the previous levels, by the 64th day there was an increase in blood values so that the hematocrit reading varied between 25.5 and 28.0%, with corresponding increases in hemoglobin and red cell count. Since there was no further rise in either reticulocytes or hematocrit value, the dose of cortisone was increased to 300 mg. a day on the 75th day.

On the 79th day, two days after a small furuncle of the scalp had developed, there appeared overnight a severe cellulitis of the orbit with chemosis, proptosis, and fixation of the globe. The temperature rose to 103.6 F. The white cell count rose to 13,900 per cubic millimeter and showed a marked shift to the left, with 47% polymorphonuclear cells, 39% band cells, 6% metamyelocytes, and 8% lymphocytes. Culture of material from the conjunctival sac yielded a hemolytic Staphylococcus aureus. Blood culture was negative.

The dose of cortisone was tapered off rapidly, so that administration of the steroid was discontinued completely on the 83d day. Penicillin (aqueous) therapy was started on the 79th day at a dose of 500,000 units every four hours and was continued through the 93d day. At the same time chloramphenicol therapy was begun. The patient received 2 gm. on the 79th day, 6 gm. on the 80th and 81st days, 5 gm. on the 82d day, 4 gm. for the next five days, 3 gm. on the 88th day, and none thereafter.

There was rapid improvement in the orbital infection, so that within 24 hours after the initiation of therapy there was a significant decrease in the tenseness and swelling about the eye. The patient's temperature subsided, and after the first 48 hours (after the 80th day) there was no further temperature elevation. The white cell count fell to 5,600 per cubic millimeter on the 82d day, with a differential count of 53% polymorphonuclear cells, 26% band cells, 18% lymphocytes, 2% basophiles, and 1% monocytes. Concomitantly, presumably owing to the cessation of cortisone therapy, the patient lost 9 lb. (4 kg.) in nine days. His reticulocyte count from the 79th to the 85th day ranged between 0.4 and 1.5%—the same range observed during the base-line periods.

On the 86th day the reticulocyte count was found to be 0.1%. On the 87th day and for the succeeding five days no reticulocytes could be found on appropriately stained cover slip preparations. On the 92d day a few reticulocytes were seen after prolonged search, and on the following day the reticulocyte count was 0.2%. On the 95th day the reticulocyte count had again reached the previous level of about 1%. There was no subsequent increase in reticulocytes above 2%.

During the period of reticulocytopenia the hematocrit reading fell from 26.0% to about 20.0%, with corresponding falls in hemoglobin and red blood cell count. At the same time a leucopenia and neutropenia developed, so that on the 87th day the white cell count was 2,750 per cubic millimeter. Serial white cell counts did not rise above 3,000 until the 94th day and did not rise above 5,000 until 12 days after that. The percentage of granulocytes fell to a low of 38 on the 89th day, when the total white cell count was 2,500 per cubic millimeter. Platelet counts, which had not been done previously, showed 94,000 per cubic millimeter on the 88th day and 66,000 on the 89th day. Eleven days later the platelet count had risen to 152,000 per cubic millimeter.

A marrow aspiration from the iliac crest done on the 88th day yielded a normoplastic marrow which was significantly different from the previous specimens in that there was a marked diminution in the proportion of the erythrogenic series, with disappearance of the erythroblastic hyperplasia previously noted. There was no suggestion of maturation arrest. There was no significant abnormality of the granulocytic series, nor were the megakaryocytes abnormal in any way.

The patient's blood values subsequently leveled off, with a hematocrit reading varying between 19.5 and 22.0%. The reticulocyte count remained around 1% and the white cell count between 4,000 and 5,000 per cubic millimeter. It was then determined to repeat the course of cortisone at 200 mg. a day for 10 days. There was a significant reticulocyte and hematocrit response to this course beginning on the 10th day, so that on the 14th day after the reinstitution of cortisone therapy the reticulocyte count reached a peak of 3.8%, and the hematocrit reading two days later reached 24.0%, with a hemoglobin level of 7.3 gm. per 100 cc. and a red cell count of 2,240,000 per cubic millimeter. It is worthy of note that after the cessation of cortisone therapy on this occasion no reticulocytopenia developed nor was there leucopenia. The hematocrit reading gradually fell back to between 21.5 and 22.0%.

The patient has been observed for about one month after the second reticulocyte response to cortisone, during which time he received 90 mg. of vitamin $B_{12}$ intramuscularly, 15 mg. a day of folic acid, and 1 gm. a day of ferrous sulfate, without significant response. As nearly as can be ascertained, there is now no significant difference in hematological status from the time he was admitted for study.

## COMMENT

Although it is obvious that this patient had a disorder of bone marrow function when first observed, his bone marrow function was found to be stable over a long period of preliminary observation. This stability was first altered by the administration of cortisone, which produced significant rises in reticulocyte count and hematocrit reading. His blood values then leveled off again, and there was no further change in bone marrow function, as measured by the reticulocyte count, during the brief period of increased dosage of cortisone or during the period when the manifestations of his complicating infection were apparent.

It was not until a week after the systemic manifestations of the infection had disappeared and the chloramphenicol therapy had been started that the reticulocyte count began to fall, and the absolute absence of reticulocytes persisted for an additional five days. It is universally accepted that reticulocytes represent cells freshly delivered from the marrow to the peripheral blood. Since the life of the reticulocyte as such is estimated to be up to four days,[4] it seems reasonable to assume that the reticulocytopenia observed in this patient was not related to bone marrow suppression consequent to his infection. The bone marrow aspiration done on the 11th day after the initiation of chloramphenicol therapy and nine days after the subsidence of the systemic manifestations of infection confirms morphologically the physiological implications of the reticulocyte counts. Without serial studies, however, no further etiological conclusions can be drawn.

The possibility that the reticulocytopenia may have resulted from cessation of the cortisone therapy does not seem reasonable. The second course of cortisone was also associated with a rise in reticulocyte count and hematocrit reading but was clearly not followed by reticulocytopenia after discontinuance of administration of the steroid. Such a reticulocytopenia following cessation of cortisone therapy has not been observed in comparable situations.

The conclusion would seem justifiable that the chloramphenicol administration was directly responsible for the fall in the reticulocyte output, which, in turn, led to the fall in hematocrit reading. The fall in total leucocytes and in neutrophiles, which has previously been reported in other patients receiving chloramphenicol,[3] in this case coincided exactly with the reticulocytopenia.

It is not clear from these observations whether the marrow depression from the chloramphenicol was a consequence of a toxic pharmacological effect of the antibiotic, perhaps associated with its nitrobenzene radical, or of an idiosyncrasy of the patient to the drug. The relatively large dosage employed in this case precludes any precise conclusions. In spite of some evidence from experimental work on dogs which suggests that the hematological effects of the drug may be related to dosage, or at least to the route of administration,[5] previous clinical observations are impressive that the toxic responses depend more on the individual patient than on the dose of chloramphenicol. Lindau [18] has reported an experimental study on human beings

4. Wintrobe, M. M.: Clinical Hematology, Ed. 3, Philadelphia, Lea & Febiger, 1951.
5. Smith, R. M.: Chloromycetin: Biological Studies, J. Bact. **55**:425, 1948.

in which, after a 30-day course of chloramphenicol in unstated dosage, only three of the eight patients showed evidence of hematopoietic depression. Smiley and associates [1e] emphasized that, as in the aplastic anemias after the use of organic arsenicals or of gold, there seems to be no relationship between the development of aplastic anemia and the size of the dose of chloramphenicol. These workers also pointed out that in two of their three cases, as well as in some other reported cases,[6] the antibiotic was given in repeated interrupted courses. It is implied by these authors that the interruption of administration may have led to sensitization of the patients' marrows. Although this possibility exists, such a method of administration was not used in this case or in several other reported cases.[7] It may be significant, however, that in all cases of fatal aplastic anemia following chloramphenicol therapy which have thus far been reported,[8] as opposed to the cases in which there has been only temporary marrow depression,[7] the intermittent form of antibiotic administration has been used.

Regardless of the occasional development of serious hematological effects from the administration of chloramphenicol, the antibiotic is considered by some authorities [9] to be the drug of choice for typhoid and perhaps for other infections in certain circumstances. It would seem reasonable that, when there are overriding indications for the use of chloramphenicol, the drug should be prescribed but with the realization that bone marrow depression, perhaps of an irreversible degree, may follow. Others [1a] have pointed out that serial white cell counts and differential counts should be made. In diseases which may previously have led to leucopenia, such white cell counts may be misleading or difficult to interpret. Furthermore, situations may arise in which the disturbance of erythropoiesis is much more marked than that of granulopoiesis. Because of the relatively long life span of the red blood cell, significant declines in hematocrit readings may not be apparent until late in the development of erythropoietic depression. Because of these considerations serial reticulocyte counts seem logical and necessary for any patient who is receiving chloramphenicol.

## SUMMARY

The course of a patient is described in which treatment with chloramphenicol was associated with temporary bone marrow depression as evidenced by declines in total leucocytes, neutrophiles, and reticulocytes. The implication of chloramphenicol as the causative agent in the marrow depression would seem justifiable.

It is suggested that chloramphenicol be administered only with the realization of its potential hematological effects, and that, in addition to total white blood cell and differential counts, serial reticulocyte counts be done during treatment with this antibiotic agent.

6. Loyd, E. L.: Aplastic Anemia Due to Chloramphenicol, Antibiotics & Chemother. **2**:1, 1952. Rich, Ritterhoff, and Hoffman.[1c]

7. Volini and associates.[1a] Gill.[1b] Lindau.[1g]

8. Footnote 2. Loyd.[6]

9. Smadel, J. E.: Chloramphenicol (Chloromycetin) in the Treatment of Infectious Diseases, Am. J. Med. **7**:671, 1949.

# HISTOPLASMA CAPSULATUM INFECTION ASSOCIATED WITH GASTRIC ULCER AND FATAL HEMORRHAGE

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AND
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THERE has been considerable interest in the literature on histoplasmosis, as the number of cases reported indicates. In 1940 only 32 cases had been reported, and by January, 1950, there were 138 cases in the literature.

This apparent increase raises the question of whether the incidence of the disease is increasing or whether clinical awareness is bringing to light hitherto unrecognized cases.

The protean manifestations and widespread systemic involvement by this condition have interested investigators since Darling first reported a case in 1906.[1] In recent years several excellent reviews have appeared [2]; so it is not the purpose of this paper to review the literature. Our purpose is to present a very interesting and unusual aspect of this disease.

## REPORT OF A CASE

The patient was a 63-year-old white, married, Italian-born man. He had lived in the Joliet, Ill., area since coming to the United States, in 1909. He was first hospitalized July 4, 1951, with a history of having had septic fever, chills, and night sweats for about two weeks. The past history revealed that 10 years previously he had had pleurisy with a cough. In 1931 he suffered a fracture of the spine. In October, 1950, he had been hospitalized with an attack of acute pain in the right upper quadrant. He recovered and was discharged in 24 hours.

Upon physical examination the patient appeared acutely ill. The blood pressure was 130/92 and the pulse rate 102. A few coarse rales were scattered throughout both lung fields. There were no palpable abdominal organs or masses.

Laboratory study revealed a red cell count of 4,410,000, with 89% hemoglobin, and a white cell count that varied between 3,000 and 5,150, with a differential count of 58% segmented

From the Departments of Medicine and Pathology, St. Joseph's Hospital, Joliet, Ill., and the Department of Pathology, Chicago Medical School.

1. Darling, S. T.: A Protozoön General Infection Producing Pseudotubercles in Lungs and Focal Necroses in Liver, Spleen, and Lymph Nodes, J. A. M. A. **46**:1283, 1906.

2. (*a*) Iams, A. M.; Tenen, M. M., and Flanagan, H. F.: Histoplasmosis in Children: Review of Literature, with Report of Case, Am. J. Dis. Child. **70**:229, 1945. (*b*) Parsons, R. J., and Zarafonetis, C. J. D.: Histoplasmosis in Man: Report of 7 Cases and a Review of 71 Cases, Arch. Int. Med. **75**:1, 1945. (*c*) Iams, A. M., and Keith, H. M.: Histoplasmosis in Infancy, J. Pediat. **30**:123, 1947. (*d*) Hodgson, C. H.; Weed, L. A., and Clagett, O. T.: Pulmonary Histoplasmosis: Summary of Data on Reported Cases and a Report on 2 Patients Treated by Lobectomy, J. A. M. A. **145**:807, 1951.

forms, 40% lymphocytes, and 2% monocytes. The platelet count was normal, and nothing abnormal was noted in a smear of the peripheral blood. Agglutination tests for typhoid, paratyphoid, and brucellosis were negative. Urinalysis showed a faint trace of albumin and fine and coarsely granular casts.

A chest x-ray revealed accentuated tracheobronchial markings in the region of the left hilus and left lower lobe. A second x-ray one week later disclosed no essential change.

The patient had a septic temperature, with daily spikes to 102 or 103 F. The pulse varied between 72 and 112 per minute. He was given a course of penicillin and chloramphenicol (chloromycetin®). For the latter, oxytetracycline ("terramycin") was later substituted. He received one blood transfusion.

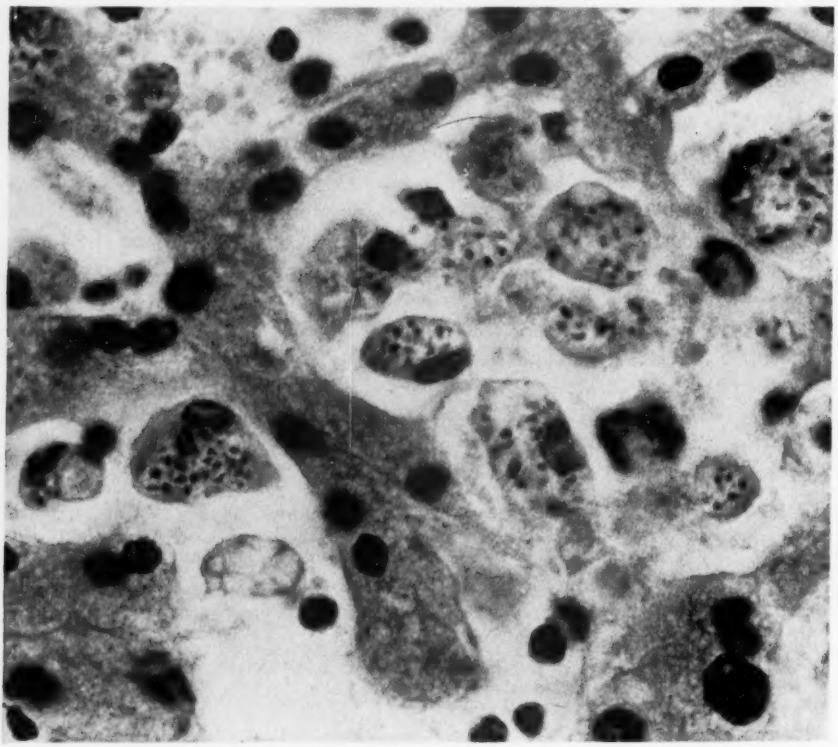

Fig. 1.—Liver, ×950, showing cells within the sinusoids containing organisms.

The temperature spikes gradually became less, but fever never completely disappeared. He was discharged on July 26, 1951, for further observation at home.

He was readmitted on Aug. 8, 1951, with a recurrence of fever and chills. Headache was now a complaint, and he had lost 15 lb. (6.8 kg.) during the present illness.

Physical examination revealed that the scattered coarse rales were present as before. The liver was enlarged, and the spleen could be felt 4 fingerbreadths below the left costal margin. It was firm, smooth, and nontender. There was no lymphadenopathy.

Laboratory work showed a red cell count of 2,750,000, with 55% hemoglobin, and 2,350 white cells, of which 75% were segmented forms, 22% lymphocytes, 2% eosinophiles, and 1% basophiles.

A chest x-ray showed markings similar to those reported on the previous examination, but there was now a fine nodulation in the left lower lung field and to a less extent in the right lower lung field.

The patient continued to have a septic fever, with spiking to 103 and 104 F. daily. Repeated small blood transfusions raised the red cell count to 3,390,000, but leucopenia persisted. Urinalysis again revealed albumin and casts. Four blood cultures on brain-heart infusion medium showed no growth after 14 days. Repeated smears for malaria were negative. The blood urea nitrogen was 57 mg. per 100 ml., and the carbon dioxide was 43.5 vol. %. Several sputa were reported as showing no acid-fast organisms, and no yeast organisms were seen on direct smear. A sternal bone marrow aspiration revealed hypoplastic marrow with no disproportion between

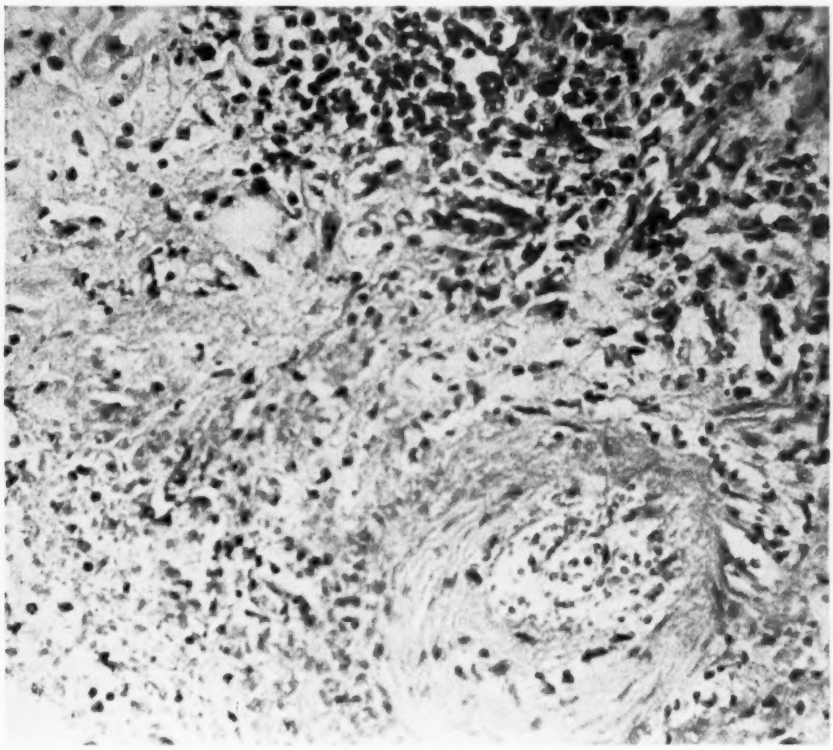

Fig. 2.—Stomach at base of ulcer, ×300. Note erosion of artery.

the erythroid and granulopoietic series. An electrocardiogram showed low-to-flat T waves in Leads I and $V_6$. T was inverted in $AV_L$. A spinal fluid examination showed no cells, a negative Kahn reaction, and no globulin. A quantitative direct van den Bergh reaction was 0.1 mg.

A week after admission edema of the ankles was noted, and the following day the patient expectorated bright-red blood. With the appearance of tachypnea, cyanosis, and inspiratory basal rales, nasal administration of oxygen was started, and he was treated with mercurials and digitalis. In addition, he received penicillin and streptomycin. A course of chloroquine was given without obvious effect on his downhill febrile course.

The evening before his death he suddenly vomited about 500 cc. of bright-red blood. Despite transfusions and supportive measures he continued to vomit blood and passed red blood per rectum. He went into shock and died.

*Necropsy.*—Only the relevant findings are presented.

Extensive adhesions were noted throughout the pleural cavities, and focal adhesions were present in the apex of the left lung. The lungs were subcrepitant, and the surface made by cutting was reddish-gray. The heart weighed 270 gm. and showed no unusual changes. The liver weighed 2,150 gm. On the cut surface it was yellowish-tan mottled with red. Grayish-white nodules measuring 1 to 2 mm. could be seen grossly. The spleen weighed 1,100 gm. and was very friable, and on sectioning the pulp was deep-red and scraped easily. Nodules similar to those noted in the liver were scattered throughout the spleen. The stomach contained blood-stained material, and on the anterior wall of the pyloric antrum near the lesser curvature was

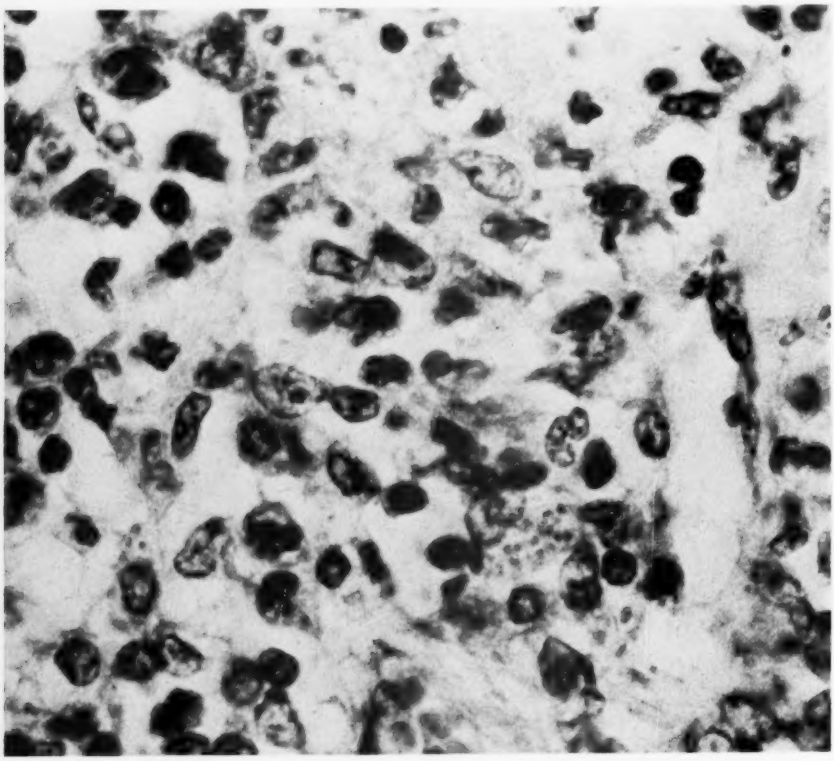

Fig. 3.—Stomach at base of ulcer, ×950. Note organisms in mononuclear cells.

a mucosal defect measuring 2.5 by 1 cm. The margins of this ulcer were raised and rolled. It was 3 mm. in depth, and the base was pale tan-gray. Adherent to the base was a blood clot. The tissues adjacent to the ulcer were thickened and edematous.

Microscopic Description: Some of the alveoli contained an exudate composed of fibrin and polymorphonuclear leucocytes. Some alveoli coalesced, while others were free of exudate. In the walls and lumina of the alveoli were large macrophages containing groups of organisms. These organisms were surrounded by capsules and had the morphology of Histoplasma capsulatum. Sections of the spleen, liver, and lymph nodes showed the presence of organisms within macrophages, which appeared to have a predilection for the reticuloendothelial system (Fig. 1).

Stomach: Sections from the stomach showed the organisms present at the base of the ulcer and infiltrating the adjoining mucosa (Figs. 2 and 3). A Gram-Weigert stain revealed the organisms to be Gram-positive (Fig. 4).

The anatomic diagnosis was as follows:

1. A generalized disseminated infection with Histoplasma capsulatum with involvement of the liver, lungs, spleen, and lymph nodes.

2. Gastric ulcer associated with Histoplasma capsulatum infection with erosion of a blood vessel.

Unfortunately, this disease was not suspected at autopsy, and cultures were therefore not obtained because the tissues had been fixed in formaldehyde.

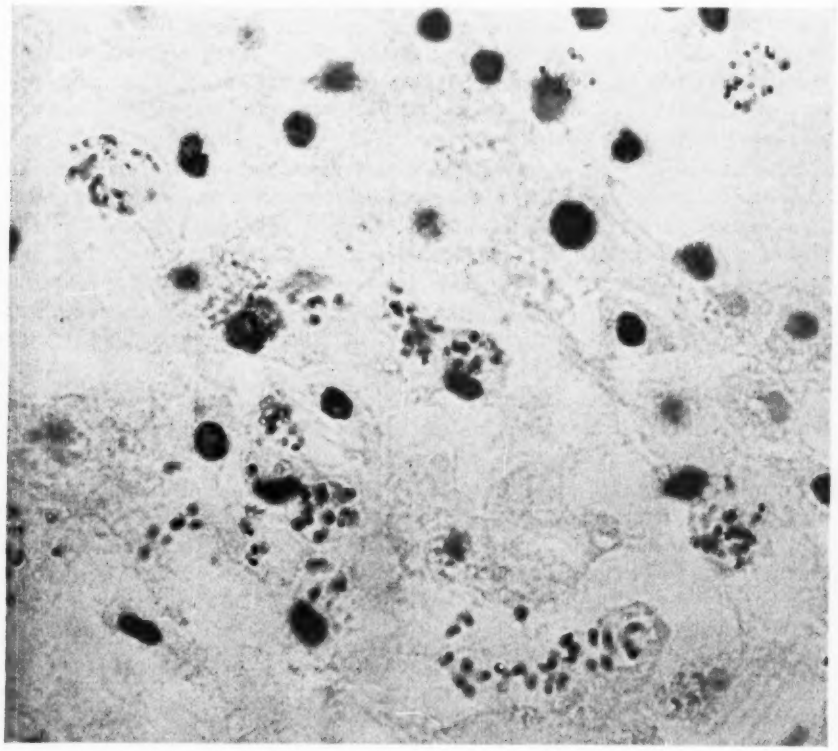

Fig. 4.—Liver, Gram-Weigert stain, ×600.

## COMMENT

This is the first case to be reported of histoplasmosis associated with an ulcerative lesion of the stomach in the human. A careful search of the literature revealed a peculiar lack of involvement of the stomach in this condition. Prior and associates [3] have recently noted gastric ulcerations in the dog. Tager and Liebow [4] have experimentally inoculated mice with the organism, and of 15 animals infected only 1 showed an invasion of the muscular coats of the stomach by parasite-laden macrophages. These authors commented on the lack of involvement of the stomach in the infection in human beings. Parsons and Zarafonetis,[2b] in their excellent

3. Prior, J. A.: Personal communication to the authors.

4. Tager, M., and Liebow, A. A.: Observations on Histoplasmosis: Induced Infection in Mouse, Yale J. Biol. & Med. **14**:469, 1942.

review, published a case of their own in which postmortem examination showed invasion of the gastric muscular wall by macrophages containing parasites. No ulcerations of the stomach were seen.

The alimentary tract has been reported to be involved in a large number of cases, with lesions being found in the oral cavity, pharynx, esophagus, liver, gall bladder, and small and large intestines.

Because of the frequent involvement of the gastrointestinal and respiratory tracts, both of these systems have been mentioned as possible portals of entry by the fungus. Allen [5] has recovered the organisms from lesions in guinea pigs and mice fed a culture of Histoplasma. His work demonstrates that the fungus can survive the gastric juice. The intestinal lesions were more conspicuous than the pulmonary in the animals infected orally.

In a review of 25 cases of gastrointestinal involvement available for careful analysis, Henderson, Pinkerton, and Moore [6] found that 8 of the patients presented a pathological picture of ulcerative enteritis. Of these, only two presented a clinical picture of chronic enteritis. The lesions were primarily in the ileum, colon, and rectum and consisted of ulcerations easily confused with those of ulcerative colitis, tuberculosis, amebic dysentery, and bacillary dysentery. The authors concluded that patients with refractory diarrhea should have stools examined for fungi, since the organism can be isolated in this manner.

The diagnosis was not made ante mortem in our case, but more persistent search for the organism by direct and cultural methods in the peripheral blood, bone marrow, and sputum might have been rewarding.

It would appear that the best methods for culture would be primary isolation in brain-heart infusion medium at room temperature. Growth of the yeast form occurs slowly, in about three to four weeks. At this time colonies are best transferred to Sabouraud's or potato-dextrose medium for a growth of another 7 to 10 days, when positive identification of the chlamydospores in the mycelial form may be made.[7] Contaminated material may best be cultured directly on Sabouraud's medium.

This case demonstrates again that the various antibiotics have no effect on the course of the disease. Neither did chloroquine appear to exert any beneficial effect in this case.

The mercurials, sulfonamides, penicillin, streptomycin, aureomycin, chloramphenicol (chloromycetin®) cycloheximide (acti-dione®), glucosulfone sodium (promine®), arsphenamine, iodides, "stilbamidine," and antimony compounds have been reported to be without effect. A note of optimism appears in the recent article of Christie and associates,[8] who used ethyl vanillate, a by-product in the manufacture of sulfite pulp. This agent has been shown to have fungicidal properties, and the

5. Allen, R. M.: Experimental Histoplasmosis, Portal of Entry of the Fungus, Am. J. Trop. Med. **28**:857, 1948.

6. Henderson, R. G.; Pinkerton, H., and Moore, L. T.: Histoplasma Capsulatum as a Cause of Chronic Ulcerative Enteritis, J. A. M. A. **118**:885, 1942.

7. Furcolow, M. L., in Peterson, J. C., Chairman: Round Table Discussion: Systemic Mycoses, Coccidioidomycosis and Histoplasmosis, Pediatrics **2**:709, 1948.

8. Christie, A.; Middleton, J. G.; Peterson, J. C., and McVickar, D. L.: Treatment of Disseminated Histoplasmosis with Ethyl Vanillate, Pediatrics **7**:7, 1951.

authors demonstrated that it inhibits the growth of Histoplasma capsulatum in vitro. They reported on 12 patients treated with the substance, 5 of whom survived and remained apparently well.

Another successful treatment from a different approach is that of Hodgson and associates.[2d] These authors report resection of the involved lobe in two cases of pulmonary histoplasmosis with apparent recovery.

Because of the reported familial incidence of this disease the patient's wife and 10 children were subjected to histoplasmin and tuberculin skin tests and chest x-rays. All members of the family professed good health except one daughter, who had had a recent cough productive of a small amount of sputum. Her chest x-ray was the only one of the group showing generalized calcifications. She afterward recovered from her cough and remained well. She was one of 3 of the group of 11 with a positive first-strength tuberculin test. One other of the group had a positive second-strength tuberculin test. Four of the group of eleven reacted positively to a 1 : 1,000 histoplasmin skin test. The remaining members had a negative skin test with a 1 : 500 dilution of histoplasmin. Two of the sons reacted positively to both histoplasmin and tuberculin.

None of the chest x-rays was considered abnormal with the exception of the one showing the calcifications mentioned and another with an appearance compatible with silicosis. The latter was that of a son who had been employed for eight years in a brick yard and had received compensation for silicosis. He was entirely asymptomatic at the time and both the histoplasmin and the tuberculin skin tests were negative.

Four positive histoplasmin reactions out of eleven tests compares well with the figures obtained by Loosli and associates[9] in their excellent study of the epidemiology of this disease. These authors found that 26.3% of students who were residents of northern Illinois reacted to histoplasmin. In addition they reported that 11.7% of those who reacted to either histoplasmin or tuberculin showed pulmonary calcifications.

## SUMMARY AND CONCLUSIONS

A case of generalized histoplasmosis is presented in which a gastric ulcer was found. The ulcer eroded a blood vessel, and the patient died from a massive gastric hemorrhage. Since the organisms were very prominent in the gastric ulcer, a possible causal relationship is suggested.

Ulceration has been reported to occur commonly in the small and large intestines but never in the human stomach. An unusual cause of gastric hemorrhage is therefore presented. A study of the patient's family revealed that the incidence of histoplasmin and tuberculin skin reactivity and presence of pulmonary calcifications were no greater than would be normally expected of lifelong residents of this geographical area.

9. Loosli, C. G.; Beadenkopf, W. G.; Rice, F. A., and Savage, L. J.: Epidemiological Aspects of Histoplasmin, Tuberculin and Coccidioidin Sensitivity, Am. J. Hyg. **53**:33, 1951.

# FLACCID QUADRIPLEGIA, HYPERKALEMIA, AND ADDISON'S DISEASE

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THE RELATION of the adrenal glands to disturbances in electrolyte metabolism in man has been the subject of extensive investigation for nearly three decades. The importance of excessive renal sodium and chloride loss in the production of many manifestations of an Addisonian crisis has been well documented by a number of observers.[1] The role of potassium in the pathogenesis of clinical signs and symptoms in patients with untreated Addison's disease has been less clearly demonstrated and at times controversial.[2] We have recently had the opportunity to observe an unsuspected case of adrenal insufficiency in which the clinical picture was intimately related to the syndrome of potassium intoxication, a syndrome that has been reported frequently in primary renal insufficiency.[3] Because of the rarity of this syndrome in Addison's disease and of the several atypical features observed in our patient, it was decided to report our case in considerable detail.

## REPORT OF CASE

G. P., a 68-year-old white retired storekeeper, entered Montefiore Hospital for the first time on May 14, 1951, complaining of inability to lift his legs of nine hours' duration and inability to move his arms of three hours' duration. The patient had been in good general health and normally active until the development of a mild upper respiratory infection on Feb. 8, 1951. Associated with this infection was the onset of anorexia and weakness which resulted in the patient's staying in bed for two weeks. On April 4, the patient had 10 carious teeth extracted. Anorexia and weak-

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1. (*a*) Loeb, R. F.: Effect of Sodium Chloride in Treatment of a Patient with Addison's Disease, Proc. Soc. Exper. Biol. & Med. **30**:808-812 (March) 1933. (*b*) Harrop, G. A.; Weinstein, A.; Sobber, L. J., and Trescher, J. H.: Diagnosis and Treatment of Addison's Disease, J. A. M. A. **100**:1850-1855 (June 10) 1933. (*c*) Kendall, E. C.: The Influence of the Adrenal Cortex on the Metabolism of Water and Electrolytes, Vitamins & Hormones **6**:277-327, 1948.

2. Wilder, R. M.; Kendall, E. C.; Snell, A. M.; Kepler, E. J.; Rynearson, E. H., and Adams, M.: Intake of Potassium, an Important Consideration in Addison's Disease: A Metabolic Study, Arch. Int. Med. **59**:367-393 (March) 1937. Zwemer, R. L., and Truszkowski, R.: The Importance of Corticoadrenal Regulation of Potassium Metabolism, Endocrinology **21**:40-49 (Jan.) 1937.

3. (*a*) Finch, C. A.; Sawyer, C. G., and Flynn, J. M.: Clinical Syndrome of Potassium Intoxication, Am. J. Med. **1**:337-352 (Oct.) 1946. (*b*) McNaughton, R. A., and Burchell, H. B.: Paralysis with Potassium Intoxication in Renal Insufficiency, J. A. M. A. **145**:481-483 (Feb. 17) 1951.

ness reappeared, and polyuria developed. On April 20, he visited his physician, who recorded his blood pressure as 146/70 and his heart rate as 40 per minute and irregular. The physician recommended that the patient partake of a high-protein diet and multivitamin capsules. Accordingly, the patient consumed 12 oz. (360 cc.) of beef extract in the next two weeks and ate a diet composed largely of meat, beef tea, and potatoes. On May 8, he felt unsteady on his feet and revisited his physician, who found no objective neurological signs. An electrocardiogram was made at this time and revealed a heart rate of 45 per minute, with an irregular rhythm; P waves were absent, and peaked T-waves could be seen (Fig. 1). His weight was now 62.3 kg., as compared with his usual weight of 66 kg. last recorded in January, 1951. Therapy consisted of parenteral administration of crude liver extract and a vitamin B complex preparation. During the next few days, the patient remained weak and complained of epigastric distress and nausea.

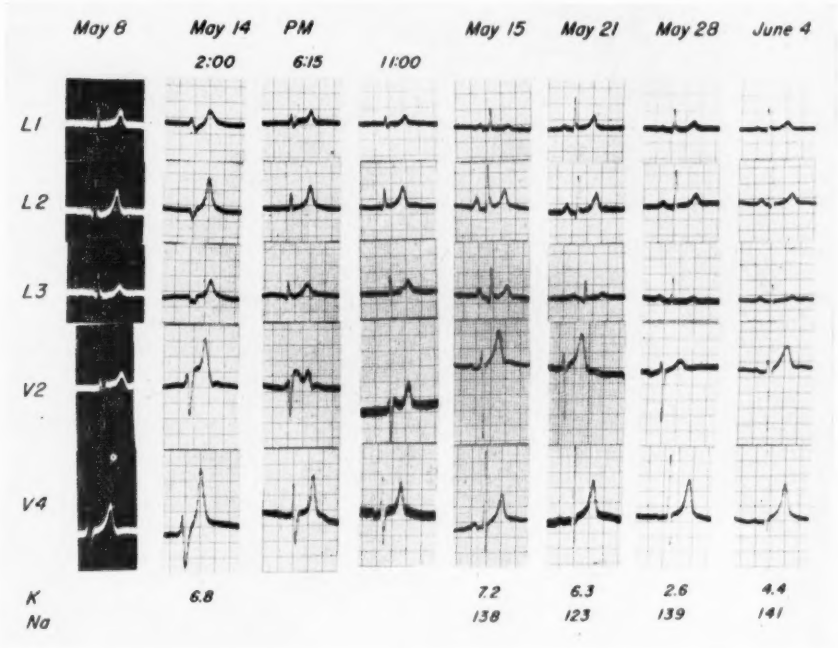


Fig. 1.—Serial electrocardiograms taken one week before (May 8) and during hospital admission. Desoxycorticosterone therapy was commenced on May 23. Observe the lack of correlation of the electrocardiographic alterations with serum potassium concentrations, whether the values are elevated or depressed.

On May 12, he complained of transient numbness of his hands and a steppage gait developed. On May 13, after breakfast, the patient became nauseated and vomited once. He voluntarily restricted his food and fluid intake for the remainder of the day. On May 14, he awoke from sleep at 3 a. m. and felt persistent numb and tingling sensations in his hands and toes. In endeavoring to arise from bed, he discovered he was paralyzed from the waist down. His physician visited him at 9:30 a. m. and noted flaccid paralysis of the lower extremities and bilateral weakness of the upper extremities. Immediate hospitalization was advised. By the time the patient arrived at Montefiore Hospital at 12:30 p. m., the paralysis had progressed to involve the upper extremities and the neck muscles.

*Past History.*—The past history was significant in several respects. In 1912, the patient was discharged from the British army with the diagnosis of pulmonary tuberculosis. He was

treated with bed rest for two months and recovered completely. In 1941, he had an attack of bronchitis and pleurisy and bed rest for one week was prescribed by his physician, who recorded his blood pressure as 122/80. It was one month before the patient regained his normal vigor. In 1947, he had a postprandial dull, aching epigastric pain which was relieved by eating. The pain persisted for several weeks. On fluoroscopy his physician observed an irregular duodenal bulb and prescribed an ulcer diet and use of antacid (Sippy) powders. The patient remained on this regimen for one month and experienced prompt relief of his pain. Although he soon abandoned this dietary regimen, his gastrointestinal symptoms did not recur. During the next two years his blood pressure was observed to vary between 134/60 and 170/90. On March 6, 1949, he had a sudden attack of syncope, and transient weakness of his right hand and dysarthria developed. He was treated with bed rest and recovered completely within four days. During this episode, his blood pressure was 170/90.

*Results of Physical Examination.*—Physical examination revealed the temperature to be 98 F., the pulse rate, 56, the respiration rate, 28, and the blood pressure, 150/80. The patient was lying motionless in bed, unable to move his arms or his legs, with the exception of his fingers, which he could partly flex, and his toes, which he could wiggle. He was rather drowsy but cooperative, coherent, and well oriented. His voice was weak. Respirations were rapid and shallow. He was staring straight up, unable to move his head either upward or to the side. The patient appeared dehydrated and showed evidence of moderate weight loss. The mucous membranes were not pigmented. There was definite brownish pigmentation of the skin over both elbows and perineal-genital area. Several dark brown freckles were observed on his upper extremities and face. Axillary hair was scanty. Aside from moderate arteriolar narrowing and arteriovenous nicking, the fundi of the eyes were normal. The mouth contained five carious upper teeth, and the pharynx was injected. The extremities were cool and dry. No significant lymphadenopathy was present. Examination of the lungs revealed transient crepitant rales over the left lower lobe posteriorly. Cardiac dulness was not increased. The cardiac rhythm was grossly irregular, with a rate of 56 per minute. The heart sounds were distant and mushy in quality. A soft blowing apical systolic murmur was heard. The abdomen was slightly distended, nontender, and tympanitic. No organs were palpable. Pubic hair was present in moderate amount. The genitalia were those of a normal man. Rectal examination revealed no abnormality.

*Results of Neurological Examination.*—Cranial nerve functions were intact except for bilateral weakness of the trapezii muscles. There was complete absence of superficial and deep reflexes in all the extremities and the abdominal musculature. Sensation to pain and touch was intact. Position sense was lost in the toes. Vibration sensation was lost in the lower extremities, including the iliac crests. There was no evidence of any sphincter disturbance.

During the physical examination, the patient's voice became weaker and respirations were more rapid and shallow. Neostigmine methylsulfate, 0.25 mg., was administered subcutaneously at 1:30 p. m. A spinal tap was performed, and 7 cc. of clear, colorless fluid was removed for analysis. An electrocardiogram was taken at 2 p. m. and was interpreted as showing evidence of hyperkalemia (Fig. 2). Blood for chemical determinations was drawn, and an intravenous infusion of 10% dextrose in isotonic sodium chloride solution was started and allowed to run slowly. No clinical change was noted in the next two hours. However, by 5 p. m., after 400 cc. of the infusion had been given, respiratory movements had become stronger and the patient was able to lift his head off the pillow. The infusion was allowed to flow more rapidly. By 5:45 p. m. the patient could move his upper extremities, and by 6:15 p. m. he could move his lower extremities. An electrocardiogram taken at 6:15 p. m. revealed decreased duration of the QRS complexes and lower T waves (Fig. 2).

*Laboratory Data.*—Extensive blood electrolyte studies are recorded in Table 1. Hematological data on admission were as follows: The hemoglobin concentration was 11.5 gm. per 100 cc.; erythrocytes numbered 4,350,000 and leucocytes, 11,800 per cubic millimeter, with a differential count of 55% neutrophiles, 37% lymphocytes, 7% eosinophiles, and 1% monocytes. Thrombocytes were 300,000. Urinalysis on admission revealed an acid reaction to litmus, a specific gravity of 1.015, a trace of albumin, no reaction for sugar, acetone, or diacetic acid.

The test for urobilinogen gave a positive result in 1:10 dilution. Two white cells and rare hyaline casts per high-power field were seen. Spinal fluid tap disclosed an initial pressure of 140 mm. and normal dynamics. The spinal fluid contained 1 lymphocyte per cubic millimeter, 30 mg. of protein and 60 mg. of sugar per 100 cc., and 120 mEq. of chloride per liter; a negative Wassermann reaction was obtained.

*Subsequent Laboratory Data.*—Liver function tests gave normal results except for a phenolsulfonphthalein (bromsulphalein®) retention of 30% in 45 minutes. The blood Wassermann reaction was negative. Urea clearance was 50% of normal on May 18. Specific gravity of

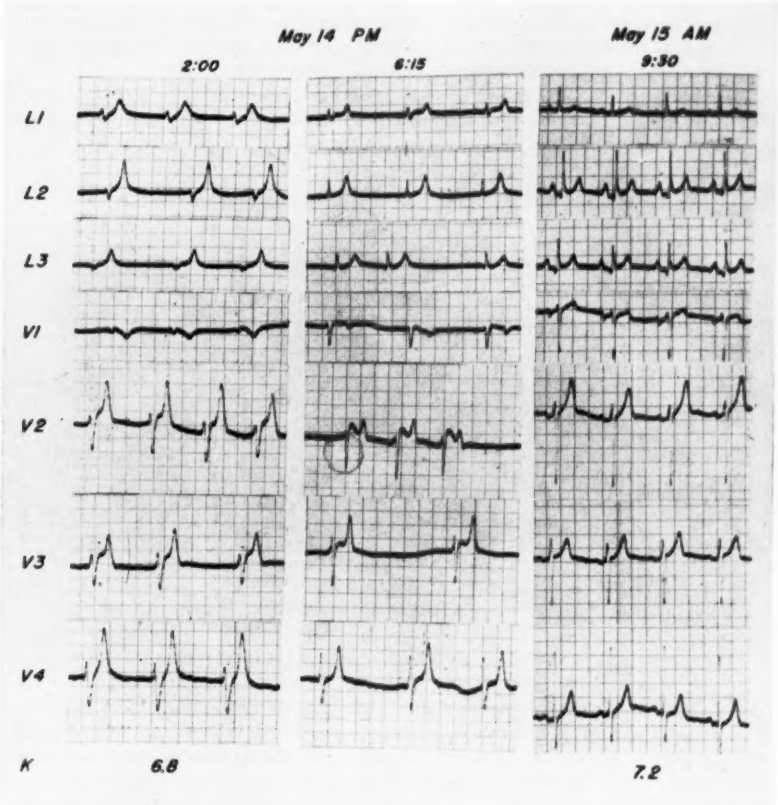


Fig. 2.—Serial electrocardiograms taken (*a*) during the period of flaccid quadriplegia before therapy at 2 p. m., (*b*) after parenteral fluid administration resulting in the disappearance of paralysis by 6:15 p. m., and (*c*) at 9:30 the next morning. Note the absence of a drop in serum potassium concentration corresponding to improvement in both the electrocardiogram and the clinical status of the patient.

random urine samples varied from 1.010 to 1.022. Twenty-four-hour urine collections showed no traces of lead or arsenic. Urine cultures were sterile, including guinea-pig inoculations for tubercle bacilli. A tuberculin hemagglutination test was negative. Stool specimens did not contain occult blood or parasites.

Repeated eosinophile counts varied from 800 to 1,200 per cubic millimeter. Three corticotropin tests for adrenocortical reserve were performed, and all resulted in a drop of eosinophiles of

less than 25% in four hours[4] (Fig. 3). The Robinson-Power-Kepler "water" test, Parts I and II, gave positive results.[5] An insulin-tolerance test, using 0.05 unit of insulin per kilogram of body weight, showed the following blood sugar values: on fasting, 82 mg.; after 30 minutes, 30 mg.; after 60 minutes, 56 mg.; after 90 minutes, 69 mg.; and after 120 minutes, 74 mg. per 100 cc. These results indicated insulin sensitivity and hypoglycemic responsiveness. The basal metabolic rate was —20%. Urinary steroid determinations were as follows: formaldehydogenic corticosteroids (determinations performed by the late Dr. K. Dobriner, of Sloan-Kettering Institute, New York), 0.5 mg. per 24 hours (normal); 17-ketosteroids, 4 mg. per 24 hours (low).

A urine specimen was examined for the presence of porphyrins. With the use of an ether extract of acidified urine, a bright red fluorescence was observed under ultraviolet light. With the Watson-Schwartz test,[6] porphobilinogen was not found in this urine. Because of the persistent finding of red fluorescence in this patient's urine, two 24-hour urine collections were analyzed chemically for porphyrins and revealed a coproporphyrin excretion of 40 γ per 24 hours, which is within normal limits (determinations performed by Dr. H. Koch, of Sloan-Kettering Institute, New York). No uroporphyrins were present.

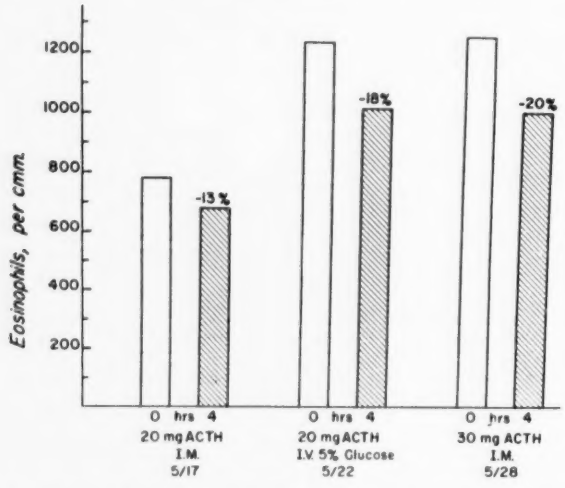


Fig. 3.—Eosinophile response following corticotropin (ACTH) administration.

*Roentgenograms.*—Roentgenograms of the chest disclosed evidence of old bilateral apical tuberculosis, with extensive thickening of the pleura over the apexes. Cardiac fluoroscopy revealed a small heart with slightly diminished pulsations. A flat plate of the abdomen did not show any calcification. Skull films were normal.

*Course.*—During the first eight hours, the patient received intravenously 3 liters of fluid containing a total of 250 mEq. of sodium chloride, 50 mEq. of sodium lactate, 300 gm. of dex-

4. Thorn, G. W.; Forsham, P. H.; Prunty, F. T. G., and Hills, A. G.: A Test for Adrenal Cortical Insufficiency: Response to Pituitary Adrenocorticotrophic Hormone, J. A. M. A. **137**:1005-1009 (July 17) 1948; correction **137**:1544 (Aug. 21) 1948.

5. Robinson, F. J.; Power, M. H., and Kepler, E. J.: Two New Procedures to Assist in Recognition and Exclusion of Addison's Disease: Preliminary Report, Proc. Staff Meet., Mayo Clin. **16**:577-583 (Sept. 10) 1941. Levy, M. S.; Power, M. H., and Kepler, E. J.: Specificity of "Water Test" as Diagnostic Procedure in Addison's Disease, J. Clin. Endocrinol. **6**:607-632 (Sept.) 1946.

6. Watson, C. J., and Schwartz, S.: A Simple Test for Urinary Porphobilinogen, Proc. Soc. Exper. Biol. & Med. **47**:393-394 (June) 1941.

trose, and 2 gm. of calcium gluconate. During this period, 1,600 cc. of urine was excreted and was found to contain 133 mEq. of sodium, 129 mEq. of chloride, and 38 mEq. of potassium, indicating positive balances with respect to sodium and chloride and a negative potassium balance. An electrocardiogram taken at 9:30 a. m. on May 15 revealed a normal sinus rhythm, normal QRS complexes, and peaked T waves (Fig. 2). Neurological examination gave normal results except for diminished vibration sensation over the tibiae bilaterally.

The patient was placed on a diet calculated to contain approximately 25 mEq. of potassium per day. For the next three days, the patient was given a daily infusion of 5% dextrose in isotonic sodium chloride solution in an attempt to facilitate renal excretion of potassium. After four days of parenteral fluid therapy, the blood urea nitrogen and serum creatinine fell to normal level; however, serum potassium remained elevated, and serum sodium and chloride values had fallen (Table). The urine output had remained between 1 and 2 liters per day, and random urine samples contained sodium and chloride concentrations of 100 mEq. per liter. Infusions were stopped at this point, and the patient was placed on a diet calculated to contain 25 mEq. of potassium and 75 mEq. of sodium chloride. During the next three days, he became anorectic and nauseated. Dehydration was evident, and his blood pressure dropped to 100/60. Although

*Blood Chemical Determinations, Electrolyte Intake, and Adrenal Steroid Therapy During Hospital Admission*

| Date | 5/14 | 5/15 | 5/16 | 5/17 | 5/18 | 5/19 | 5/20 | 5/21 | 5/22 | 5/23 | 5/24 | 5/25 | 5/26 | 5/27 | 5/28 | 5/29 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Urea nitrogen, mg./100 cc.. | .... | 54.8 | .... | .... | 15.5 | .... | .... | 27 | .... | .... | .... | 14.2 | .... | .... | .... | .... |
| Creatinine, mg./100 cc..... | .... | 2.4 | .... | .... | 1.6 | .... | .... | 2.1 | .... | .... | .... | 1.5 | .... | .... | .... | .... |
| Serum calcium, mg./100 cc.. | 10.6 | 11.0 | .... | .... | .... | .... | .... | .... | .... | .... | .... | 10.2 | .... | .... | .... | .... |
| Serum phosphorus, mg./100 cc. ..... | .... | 4.8 | .... | .... | .... | .... | .... | .... | .... | .... | .... | 3.0 | .... | .... | .... | .... |
| Serum sodium, mEq./L. ... | .... | 138 | 134 | .... | 128 | .... | .... | 123 | .... | 126 | 130 | 132 | .... | 135 | 139 | 139 |
| Serum potassium, mEq./L. | 6.8 | 7.2 | 7.0 | 6.6 | 6.7 | .... | .... | 6.3 | .... | 5.7 | 5.2 | 5.0 | .... | .... | 2.6 | 3.0 |
| Serum carbon dioxide, mEq./L. ..... | 15.1 | 17.6 | .... | .... | 25.3 | .... | .... | .... | .... | 22.7 | .... | 25.8 | .... | .... | 26.8 | .... |
| Serum chloride, mEq./L.... | 101 | 96.6 | .... | .... | 90.0 | .... | .... | 86.0 | .... | 91.2 | 96.7 | 96.2 | .... | 98.6 | 99.4 | 99.8 |
| DOCA therapy, mg. ..... | .... | .... | .... | .... | .... | .... | .... | .... | .... | 5 | 10 | 10 | 10 | 10 | .... | .... |
| Sodium chloride intake, mEq. ..... | 250 | 175 | 175 | 175 | 75 | 75 | 75 | 75 | 180 | 180 | 180 | 180 | 180 | 180 | 180 | 180 |
| Potassium intake, mEq.... | 0 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |

the patient complained of muscular weakness, no objective neurological signs were present. High levels of urinary sodium chloride persisted and resulted in a drop of serum sodium to 123 mEq. and of chloride to 86 mEq. per liter; serum potassium remained elevated at 6.3 mEq. per liter. Because of the patient's progressively downward clinical course, it was decided to ascertain whether, with a high sodium chloride intake, desoxycorticosterone acetate could reduce the renal salt loss.[7] Accordingly, he was placed on a basic low-sodium diet containing 16 mEq. of sodium chloride and 25 mEq. of potassium and was given 154 mEq. of sodium chloride in tablet form. Desoxycorticosterone acetate was administered intramuscularly as shown in Figure 4 and resulted in a diminution in renal excretion of sodium, chloride, and water and an increase in urinary potassium output. Figure 4 also illustrates that with this decreased urinary sodium excretion there occurred a drop in hematocrit, a rise in blood pressure, a gain in weight, and a fall in the salivary sodium-potassium ratio. The patient became stronger, regained his appetite, and was out of bed walking about by the fourth day of the study. His serum sodium and chloride levels rose to normal, and his serum potassium fell to 2.6 mEq. per liter (Table). No significant electrocardiographic alterations were associated with this low serum potassium value, except for a decrease in the amplitude of the T wave in Lead $V_2$ (Fig. 1). Immediately after cessation of desoxycorticosterone therapy, 150 mg. of cortisone was administered parenterally over a 24-hour period. Urinary sodium and chloride loss increased markedly, and the eosinophile count fell from 1,050 to 77 per cubic millimeter in 24 hours.

7. Thorn, G. W.; Koepf, G. F., and Clinton, M., Jr.: Renal Failure Simulating Adrenocortical Insufficiency, New England J. Med. **231**:76-85 (July 20) 1944.

*Subsequent Course.*—The patient was discharged with instructions to take a regular diet, 3 gm. of sodium chloride in tablet form, and 5 mg. of desoxycorticosterone acetate parenterally a day. After six days on this regimen, ankle edema and mild hypertension developed. The dose of desoxycorticosterone was reduced to 2.5 mg. every other day, and the edema and hypertension disappeared. The patient did well on this regimen throughout the summer and fall. In October, 1951, the 2.5-mg. injections of desoxycorticosterone were reduced to two a week. In December, 1951, the patient complained of pain in his shoulder and knee joints. By this time,

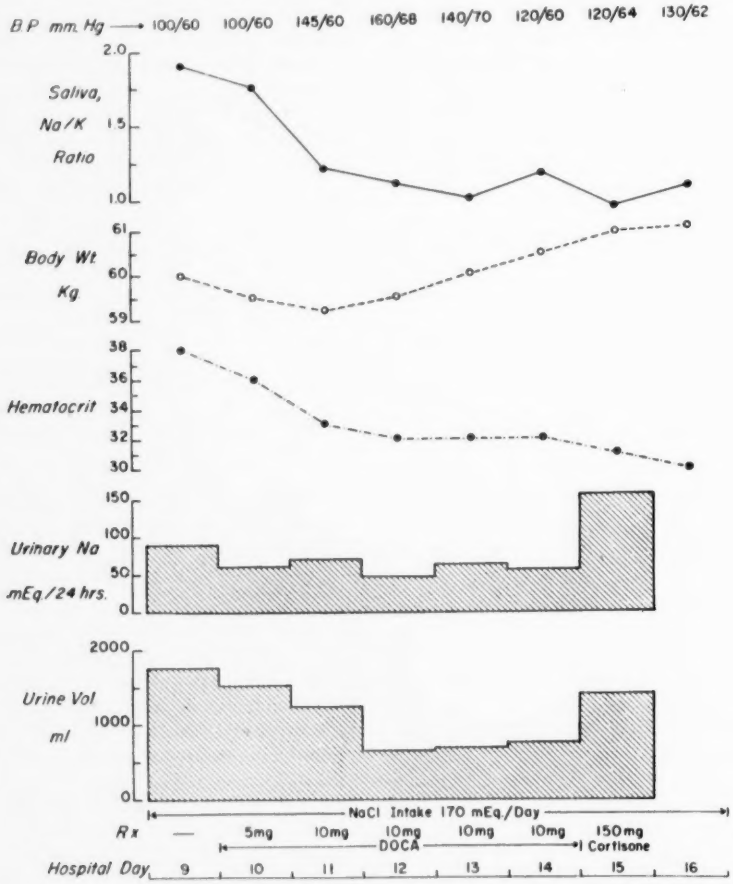


Fig. 4.—Clinical and metabolic response to adrenal steroid therapy.

brown pigmentation had become easily noticeable, particularly on the skin over his neck and chest. On Dec. 24, administration of 25 mg. of corticotropin resulted in a 40% drop in eosinophiles in four hours. Desoxycorticosterone injections and use of salt tablets were stopped for five days. During this period, the patient complained of epigastric distress, anorexia, muscular weakness, and headache. His blood pressure dropped from 126/70 to 112/60; he lost 1 kg. in weight; his serum sodium fell from 134 to 129 mEq. per liter; his blood urea nitrogen rose from 25 to 35.6 mg. per 100 cc. He was given 10 mg. of desoxycorticosterone parenterally and 7 gm. of salt in tablet form. Within 24 hours, the patient felt stronger and his epigastric distress, headache, and joint pains disappeared. He was given 2.5 mg. of desoxycorticosterone,

3 gm. of salt in tablet form, and 25 mg. of cortisone orally per day. With this regimen, he had a good appetite, gained 2 kg. in weight in three weeks without evidence of edema formation, and felt better than he had in years. The cortisone dosage was reduced to 6.25 mg. per day by mouth, and that of desoxycorticosterone to 3 mg. every three days intramuscularly. With this treatment, the patient has continued to do well.

COMMENT

The question arises of the relation of the disturbances in electrolyte metabolism, the flaccid quadriplegia, and the abnormal electrocardiographic changes encountered in this case. On the basis of the electrocardiogram made on May 8 (Fig. 1), it seems logical to assume that hyperkalemia was present for at least one week prior to his admission to the hospital. The combination of persistent hyperkalemia and inability of the renal tubules to conserve sodium in spite of low serum levels suggested that our patient had either primary renal disease of the salt-losing type or adrenal insufficiency. From the clinical course, it soon became evident that there was a marked dissociation between the serum creatinine and blood urea nitrogen, on one hand, and the serum potassium, sodium, and chloride values, on the other. Random specific gravity determinations on the urine were as high as 1.022. After the administration of desoxycorticosterone acetate, there occurred a diminution in urinary sodium and an increase in urinary potassium excretion, suggesting that the renal tubules were capable of responding to this synthetic hormone and excluding the possibility of a salt-losing nephritis.[7]

In keeping with the diagnosis of adrenal insufficiency for our patient were the past history of pulmonary tuberculosis, scanty axillary hair, pigmentation of the skin, the smallness of the heart, absence of ketonuria in spite of marked dehydration, positive results on the water test, low basal metabolic rate, low urinary 17-ketosteroid excretion, high eosinophile counts, eosinophile drop of less than 50% four hours following the injection of corticotropin, and the good clinical and biochemical response associated with sodium chloride and desoxycorticosterone therapy, including a prompt fall in salivary sodium-potassium ratio.[8]

However, there are certain atypical features of our case which at first perusal seem to be inconsistent with the diagnosis of Addison's disease. These include the absence of hypotension and hypoglycemic manifestations, a normal response to insulin-induced hypoglycemia, and a normal 24-hour urinary corticosteroid excretion. In persons of the older age group, Thorn has remarked that advanced adrenal insufficiency may not be accompanied with hypotension.[9] Our patient had an antecedent history of mild hypertension, and, after stabilization on a desoxycorticosterone and salt regimen, systolic levels as high as 150 mm. have been repeatedly observed. Not all cases of Addison's disease necessarily have hypoglycemia as a major manifestation.[10] Hypoglycemic responsiveness following insulin adminis-

8. Frawley, T. F., and Thorn, G. W.: The Relation of the Salivary Sodium-Potassium Ratio to Adrenal Cortical Activity, in Proceedings of the Second Clinical ACTH Conference, Vol. I: Research, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, pp. 115-222.

9. Thorn, G. W.; Forsham, P. H., and Emerson, K., Jr.: The Diagnosis and Treatment of Adrenal Insufficiency, Springfield, Ill., Charles C Thomas, Publisher, 1949, p. 31.

10. Ward, E.; Parkin, T. W., and Howell, L. P.: Diabetes Mellitus and Addison's Disease: Report of Case with Normal Urinary Corticosteroids and High Insulin Requirement, Proc. Staff Meet., Mayo Clin. **25**:145-149 (March 29) 1950. Thorn, G. W.; Koepf, G. F.; Lewis, R. A., and Olsen, E. F.: Carbohydrate Metabolism in Addison's Disease, J. Clin. Invest. **19**:813-832 (Nov.) 1940.

tration depends not only upon the release of corticosteroids by the adrenal cortex but also upon a mobilizable store of liver glycogen [11] and the ability of the adrenal medulla to release epinephrine.[12] In a large series of observations, Talbot and associates have noted several patients with Addison's disease who excreted normal amounts of urinary corticosteroids.[13] This finding has led to the thesis that some patients with hypoadrenocorticalism are suffering from a partial rather than a total inability to produce corticosteroids. The observations in our patients of an inability to excrete a water load at a normal rate [14] and a drop in eosinophiles of less than 50% following corticotropin administration [4] are in keeping with this thesis.

In considering the causation of the flaccid quadriplegia, the presence of normal cerebrospinal fluid findings and the clinical course seem to be strong evidence against a primary organic lesion of the central nervous system and are more in keeping with a metabolic disturbance of the peripheral neuromuscular system. The bright red fluorescence under ultraviolet light of an ether extract of acidified urine specimens suggested the presence of porphyrin. However, chemical analysis of these same urine specimens did not reveal the presence of porphobilinogen, uroporphyrins, or an excessive excretion of coproporphyrins, thus illustrating the nonspecificity of the above test for urinary porphyrins. Although excessive urinary salt loss has been described in acute porphyria,[15] the available evidence in the literature indicates that there is hyperfunction, rather than hypofunction, of the adrenal gland during the acute stage.[16]

Flaccid quadriplegia, rapid in onset and ascending in type, has been described by Finch and colleagues in their description of the clinical syndrome of potassium intoxication.[3a] The establishment of the diagnosis of this syndrome depends upon the demonstration of characteristic electrocardiographic alterations, as well as an elevated serum potassium. All these changes were present in our patient.

Although intravenous administration of dextrose and saline solution has been described as effective therapy in this syndrome, an interesting feature in our patient was the absence of a drop in serum potassium corresponding to the disappearance of the paralysis and the return of the electrocardiogram to a more normal pattern. This observation is not as disturbing as it first seems; for it has become increasingly evident in recent years that the correlation of serum potassium with electrocardiographic changes may be statistically significant, but that this correlation does not

11. Soskin, S.; Essex, H. E.; Herrick, J. F., and Mann, F. C.: The Mechanism of Regulation of Blood Sugar by the Liver, Am. J. Physiol. **124**:558-567 (Nov.) 1938.

12. Beath, A. G.; Billing, B., and Sherlock, S.: The Effect of Adrenaline and Noradrenaline on Hepatic Blood Flow and Splanchnic Carbohydrate Metabolism in Man, J. Physiol. **115**:430-441 (Dec.) 1951.

13. Talbot, N. B.; Wood, M. S.; Worcester, J.; Christo, E.; Campbell, A. M., and Zygmuntowicz, A. S.: Further Observations on the Urinary Excretion of Water-Soluble Corticosteroids by Normal and Abnormal Subjects, J. Clin. Endocrinol. **11**:1224-1236 (Nov.) 1951.

14. Slessor, A.: Studies Concerning the Mechanism of Water Retention in Addison's Disease and in Hypopituitarism, J. Clin. Endocrinol. **11**:700-723 (July) 1951.

15. Linder, G. C.: Salt Metabolism in Acute Porphyria, Lancet **2**:649-652 (Nov. 1) 1947.

16. Prunty, F. T. G.: Sodium and Chloride Depletion in Acute Porphyria with Reference to the Status of Adrenal Cortical Function, J. Clin. Invest. **28**:690-699 (July) 1949.

always hold for individual cases.[17] In a critical review, Kendall has emphasized the lack of correlation between the harmful effects of potassium administration and serum potassium levels and the beneficial effects produced by sodium chloride in adrenal insufficiency.[1c]

In agreement with the premise that the electrocardiogram reflects the state of the tissues more reliably than the serum potassium level, several investigators have expressed the view that the intracellular potassium content is the most important factor in determining both the electrocardiographic and the clinical state of the patient.[18] This concept has been discussed particularly in reference to the clinical problems of potassium deficiency. That this concept is too simple to be accepted is revealed by Miller and Darrow's work which showed that, within wide limits, the amount of potassium in the muscle cells does not limit the capacity of rats to swim continuously for 60 minutes.[19]

In adrenal insufficiency in animals and in man, marked electrocardiographic changes associated with hyperkalemia have been observed. Winkler and co-workers noted electrocardiographic changes during spontaneous potassium poisoning in adrenalectomized dogs similar to those seen in our patient.[20] Nicholson and Soffer observed auricular fibrillation in adrenalectomized dogs with an elevated serum potassium.[21] When these dogs were given only sodium chloride solutions intravenously, a normal sinus rhythm appeared. In infants with congenital adrenal hyperplasia and adrenal insufficiency of the sodium-potassium hormone type, hyperkalemia, absent P waves, and intraventricular block have been recorded.[22]

Tissue analyses in several species of adrenalectomized animals have shown that excess potassium is retained not only in the extracellular fluid but also in certain tissue fluids, including skeletal and cardiac muscle.[23] The reasons for this increased

17. Levine, H. D.; Merrill, J. P., and Somerville, W.: Advanced Disturbances of the Cardiac Mechanism in Potassium Intoxication in Man, Circulation **3**:889-905 (June) 1951. Tarail, R.: Relation of Abnormalities in Concentration of Serum Potassium to Electrocardiographic Disturbances, Am. J. Med. **5**:828-837 (Dec.) 1948. Nadler, C. S.; Bellet, S., and Lanning, M.: Influence of Serum Potassium and Other Electrolytes on the Electrocardiogram in Diabetic Acidosis, ibid. **5**:838-848 (Dec.) 1948.

18. Marks, L. J.: Potassium Deficiency in Surgical Patients, Ann. Surg. **132**:20-35 (July) 1950. Currens, J. H., and Crawford, J. D.: The Electrocardiogram and Disturbance of Potassium Metabolism, New England J. Med. **243**:843-850 (Nov. 30) 1950. Merrill, A. J.: The Significance of the Electrocardiogram in Electrolyte Disturbances, Am. Heart J. **43**:634-639 (April) 1952.

19. Miller, H. C., and Darrow, D. C.: Relation of Serum and Muscle Electrolyte, Particularly Potassium, to Voluntary Exercise, Am. J. Physiol. **132**:801-809 (April) 1941.

20. Winkler, A. W.; Smith, P. K., and Hoff, H. E.: Spontaneous Potassium Poisoning in the Adrenalectomized Animal, Federation Proc. **1**:94 (March) 1942.

21. Nicholson, W. M., and Soffer, L. J.: Cardiac Arrhythmia in Experimental Suprarenal Insufficiency in Dogs, Bull. Johns Hopkins Hosp. **56**:236-243 (April) 1935.

22. Kyle, L. H., and Knop, C. Q.: Simulation of Cardiac Disease by Adrenocortical Failure in Infants, New England J. Med. **243**:681-690 (Nov. 2) 1950.

23. Harrison, H. E., and Darrow, D. C.: The Distribution of Body Water and Electrolytes in Adrenal Insufficiency, J. Clin. Invest. **17**:77-86 (Jan.) 1938. Darrow, D. C.; Harrison, H. E., and Taffel, M.: Tissue Electrolytes in Adrenal Insufficiency, J. Biol. Chem. **130**:487-502 (Oct.) 1939. Muntwyler, E.; Mellors, R. C.; Mautz, F. R., and Mangun, G. H.: Electrolyte and Water Equilibria in the Dog: II. Electrolyte and Water Exchange Between Skeletal Muscle and Blood in Adrenal Insufficiency, ibid. **134**:367-387 (June) 1940.

cellular potassium content are not known, although the two most popular theories concern primary renal retention of potassium, with a secondary increase in cellular potassium,[24] and a primary abnormal cellular membrane permeability to potassium due to the specific absence of the adrenal cortical hormone(s).[25] Regardless of which theory is correct, it is evident that the potassium content of the diet is an important factor in determining how much potassium an adrenalectomized animal will retain in its body fluids. Darrow has observed low muscle potassium values in rats with chronic adrenal insufficiency maintained on a potassium-deficient diet.[26]

In human beings with Addison's disease, the problem of severe potassium intoxication is uncommon.[27] It is important to remember that these patients are often anorectic and nauseated, frequently vomit, and may have diarrhea. These factors could cause a net deficit of body potassium in spite of renal retention of this cation. In keeping with this thesis, Burrows and Sisson have observed low exchangeable potassium values in two patients with Addison's disease; one was untreated.[28] One of us has recently observed a child (through the courtesy of Dr. C. D. Cook) with untreated Addison's disease, who was markedly deficient in potassium as demonstrated by electrocardiographic changes, inability to conserve sodium until potassium was administered in large amounts, and a low exchangeable potassium level.

A review of the clinical history of our patient reveals that the high protein diet and the beef broth concentrate which he consumed for three weeks prior to the onset of the paralysis served as extremely rich sources of potassium. Chemical analysis of the beef extract has revealed a potassium content of 25.5 mEq. per ounce (30 cc.),[29] and our patient admitted consuming at least 12 oz. A high potassium intake coupled with a persistent reduction in renal excretion of this cation would soon allow a person to go into positive potassium balance, resulting in the accumulation of potassium in both the extracellular and the intracellular fluids. Nicholson and Spaeth have observed that severe muscular weakness may be precipitated in Addison's disease by the giving of a potassium salt.[30] In their patient the oral administration of 2 gm. of potassium chloride resulted in the development of an Addisonian crisis, with severe generalized muscle weakness and a serum potassium of 6.6 mEq. per liter. After vigorous therapy with adrenal cortex extract, desoxycorticosterone, and saline infusions, the patient regained his muscular strength. Unfortunately, electrocardiograms and careful electrolyte studies were not recorded in this case.

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24. Harrison, H. E., and Darrow, D. C.: Renal Function in Experimental Adrenal Insufficiency, Am. J. Physiol. **125**:631-643 (April) 1939.

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26. Darrow, D. C.: Tissue Water and Electrolyte, Ann. Rev. Physiol. **6**:95-122, 1944.

27. Somerville, W.; Levine, H. D., and Thorn, G. W.: The Electrocardiogram in Addison's Disease, Medicine **30**:43-79 (Feb.) 1951.

28. Burrows, B. A., and Sisson, J. H.: The Measurement of Total Body Potassium by Radioisotope Dilution Technique, J. Clin. Invest. **29**:801-802 (June) 1950.

29. McCance, R. A., and Widdowson, E. M.: The Chemical Composition of Foods, Brooklyn, Chemical Publishing Company, Inc., 1947.

30. Nicholson, W. M., and Spaeth, W.: Some Clinical Manifestations of Abnormal Potassium Metabolism, South. M. J. **42**:77-83 (Feb.) 1949.

We did not consider it safe to administer potassium experimentally to our patient because of the possibility of recurrence of the paralysis or the precipitation of an Addisonian crisis.

SUMMARY

A case of adrenal insufficiency, presenting the clinical picture of severe potassium intoxication, including flaccid quadriplegia, is recorded because of the rarity of such a condition. The lack of correlation between the electrocardiographic and clinical manifestations, on the one hand, and the serum potassium levels, on the other, was striking, whether the serum potassium was elevated (7 mEq. per liter) or depressed (2.6 mEq. per liter). The importance of a high potassium intake in the production of this clinical syndrome is emphasized.

1111 Smithfield Ave. (Dr. Marks).

Dr. Abraham White and Mr. George Ross performed studies on blood, urine, and salivary electrolyte concentrations.

# AUREOMYCIN, CHLORAMPHENICOL, AND OXYTETRACYCLINE ("TERRAMYCIN") IN MUMPS

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AND
Z. B. BARNES, M.D.
MEMPHIS

AFTER THE appearance of preliminary reports of favorable effects of aureomycin, chloramphenicol, and oxytetracycline ("terramycin") in mumps, these three broad-spectrum antibiotics were studied systematically for symptomatic effects when given early in the course of mumps orchitis. A clear demonstration of therapeutic results was considered desirable because epidemic parotitis was the most frequent infection of known viral etiology in a medical service for adults and was often associated with distressing symptoms. Mumps orchitis was found to present a course severe enough and consistent enough to allow conclusions to be drawn from a few cases in which the symptoms persisted despite therapy.

## LITERATURE

*Aureomycin.*—Tentative reports of favorable results of aureomycin therapy in mumps were made by four groups of investigators. Langley and Bryfogle [1] treated three patients with parotitis on the first, third, and seventh days of illness with symptomatic improvement four, five, and two days, respectively, after treatment was begun. Schmuttermeier, Swoboda, and Thalhammer [2] treated one patient with parotitis and bilateral orchitis with aureomycin on the seventh day of disease. The treatment was begun four days after the onset of left orchitis and on the day of onset of right orchitis. Both swellings disappeared in two more days. Spinelli, Cressy, and Kunkel [3] treated four patients with mumps orchitis on the second, first, fourth and seventh days, respectively, with disappearance of fever and symptoms in 32 to 36 hours after therapy in all. Testicular swelling disappeared within three days. Schaub [4] reported 11 cases of parotitis in adults treated with aureomycin,

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1. Langley, W. D., and Bryfogle, J.: Aureomycin in Epidemic Parotitis, J. A. M. A. **143**:1333-1334, 1950.

2. Schmuttermeier, E.; Swoboda, W., and Thalhammer, O.: Aureomycin bei kompliziertem Mumps des Erwachsenen, Wien. klin. Wchnschr. **62**:979-980, 1950.

3. Spinelli, N. P. R.; Cressy, N. L., and Kunkel, P.: Aureomycin in the Treatment of Mumps Orchitis and Encephalitis, Connecticut M. J. **15**:113-116, 1951.

4. Schaub, F.: Aureomycin beim Mumps des Erwachsenen, Praxis **40**:711-712, 1951.

compared with 11 untreated controls. In none of the cases of treated parotitis did the condition progress to pancreatitis or orchitis, but in two of the control cases pancreatitis developed and in one orchitis developed. Aureomycin was administered to four patients after the appearance of orchitis and to two after the appearance of pancreatitis. These six patients had a shorter average hospitalization, a shorter febrile course, a greater proportion of normal sedimentation rates, a shorter period of abnormal local findings, and a better final result than six comparable controls.

Evidence against the clinical effectiveness of aureomycin was found in four investigations. Two groups of investigators observed failures to prevent mumps by treatment with aureomycin during the incubation period. Shane and Sodero [5] saw the onset of parotitis in a patient treated with a seven-day course of aureomycin totaling 14 gm. for pleurisy with effusion following tonsillectomy. The onset of epidemic parotitis occurred the day after administration of aureomycin was discontinued. Mazursky, Wright, and Weichsel [6] observed the onset of parotitis in 2 of 82 patients with varicella who were treated for three days each with aureomycin. The completion of aureomycin treatment preceded the onset of parotitis by 11 and 12 days, respectively, in these two patients. Pitman and associates,[7] described the onset of orchitis in one patient while large doses of aureomycin, penicillin, and a sulfonamide compound were being administered. Kerr and Shaw [8] reported that a trial of aureomycin therapy in mumps meningitis was "inconclusive."

*Chloramphenicol.*—Two groups of authors qualified their statements as to the effectiveness of chloramphenicol therapy in epidemic parotitis by emphasizing the limited number of their observations. Chloramphenicol was reported by Redewill [9] in the successful treatment of one patient with bilateral parotitis and left orchitis in whom the administration of 4 gm. of chloramphenicol, followed by one capsule every 3 hours, led to disappearance of the swelling in 26 hours and ambulation in 3 days. Ghalioungui [10] reported four cases of parotitis in which treatment with chloramphenicol was begun 2½ days, 5 days, 2 days, and 36 hours after onset, respectively. The patients became symptom-free in 36 hours, 48 hours, 48 hours, and 8 days, respectively, after therapy was begun.

*Oxytetracycline ("Terramycin").*—The reported results of the treatment of epidemic parotitis with oxytetracycline presented a confusing picture. One controlled study of oxytetracycline therapy in epidemic parotitis was made by Caldwell, Spies, Wolfe, Lepper, and Dowling [11] in nine treated patients compared with nine comparable controls. No difference was seen in the course of the disease with and

5. Shane, S. J., and Sodero, G. W.: Aureomycin and Mumps, Canad. M. A. J. **63**:387-388, 1950.

6. Mazursky, M. M.; Wright, L., and Weichsel, M.: Clinical Observations on the Use of Aureomycin in Varicella, Pediatrics **5**:276-279, 1950.

7. Pitman, E. R.; Blumenfeld, S.; Perlman, A., and Boyd, L. J.: Mumps with Parotitis, Meningo-Encephalitis, and Orchitis: Report of a Case, Bull. New York M. Coll. **13**:62-67, 1950.

8. Kerr, W. J., and Shaw, E. B.: Diseases of the Central Nervous System: Symposium; The Diagnosis and Treatment of Meningitis, California Med. **73**:325-331, 1950.

9. Redewill, F. H.: Chloromycetin in the Successful Treatment of Recurring Epididymitis, J. Urol. **62**:581-587, 1949.

10. Chloramphenicol in Mumps, Letters to the Editor, Lancet **2**:75-76, 1950.

11. Caldwell, E. R.; Spies, H. W.; Wolfe, C. K.; Lepper, M. H., and Dowling, H. F.: The Treatment of Various Infections with Terramycin, J. Lab. & Clin. Med. **36**:747-753, 1950.

without treatment with oxytetracycline. The other two groups of authors reported favorable results with oxytetracycline in cases of orchitis. Sayer, Michel, Mall, and Kirby [12] treated two patients with mumps orchitis beginning on the fourth and fifth day, with prompt disappearance of symptoms. They stated that evaluation was difficult owing to the variable course of the disease. Willcox [13] reported on one patient with mumps complicated by orchitis treated with oxytetracycline on the second day of orchitis who was observed again on the sixth day after onset of orchitis and found normal.

The clinical data on the effects of aureomycin, chloramphenicol, and oxytetracycline in treatment of mumps were amplified by laboratory studies in the case of aureomycin and of chloramphenicol. Aureomycin in preliminary experiments by Wong and Cox [14] with mumps-virus-infected chick embryos reduced or completely inhibited the production of virus as measured by the hemagglutinating activity of the virus (allantoic fluid) for chicken red cells but had no effect on rate of multiplication and infective titer of the mumps virus as measured by infectivity tests carried out on embryonated hens' eggs. Chloramphenicol was used by McLean, Schwab, Hillegas, and Schlingman [15] to treat infected eggs. No effect was observed on the proliferation of the mumps virus in eggs. No experimental studies of oxytetracycline antivirus activity were reported in which mumps virus was employed. In general, these and other workers found that filtrable viruses of small size, other than mumps virus, proved resistant to the antivirus activities of aureomycin, chloramphenicol, and oxytetracycline whenever they were tested in vitro or in vivo.

In summary, the evidence in the medical literature for the therapeutic effectiveness of aureomycin, chloramphenicol, or oxytetracycline in treatment of mumps was not clear, despite the appearance of several reports. Summaries in the literature reflected the confusing evidence. Keefer [16] classified the evidence for therapeutic activity of the three antibiotics in mumps as "questionable." Long [17] used the words "little value." Yow [18] made an unequivocal statement that aureomycin and chloramphenicol were "not effective" in mumps.

## CHOICE OF CASES FOR TREATMENT

Symptom analysis in a relatively large series of untreated patients in the literature and comparisons with untreated patients seen in this hospital led us to conclude that the course of mumps in most cases was too mild and too variable to be readily

12. Sayer, R. J.; Michel, J. C.; Mall, F. C., and Kirby, W. M. M.: Terramycin: Clinical, Pharmacological, and Bacteriological Studies, Am. J. M. Sc. **221**:256-263, 1951.

13. Willcox, P. R.: A Case of Mumps Orchitis Treated with Terramycin, M. Press **226**:261-262, 1951.

14. Wong, S. C., and Cox, H. R.: Action of Aureomycin Against Experimental Rickettsial and Viral Infections, Ann. New York Acad. Sc. **51**:290-303, 1948.

15. McLean, I. W.; Schwab, J. L.; Hillegas, A. B., and Schlingman, A. S.: Symposium on Antibiotics: Susceptibility of Micro-Organisms to Chloramphenicol (Chloromycetin), J. Clin. Invest. **28**:953-963, 1949.

16. Keefer, C. S.: Antibiotics Up to Date, Merck Rep. **61**:3-8, 1952.

17. Long, P. H.: The Use and Importance of Antibiotic Therapy, Pennsylvania M. J. **53**:209-218, 1950.

18. Yow, E. M.: Clinical Indications for and Administration of Aureomycin and Chloromycetin, M. Rec. & Ann. **44**:293, 1950.

used in judging the effectiveness of therapy. The analyses demonstrated, however, that epidemic parotitis with orchitis had a course sufficiently severe and predictable to serve as a test of therapy.

The multiple manifestations of mumps were described fully by several authors. The representative reports of Eagles [19] and McGuinness and Gall [20] are quoted hereafter. The general characteristics of mumps were as follows. Parotid-gland involvement occurred most frequently and was bilateral in 70% of the patients. Combined submaxillary- and parotid-gland involvement occurred in about 12%. The onset of parotitis was usually moderately acute, with malaise, headache, fever, chilliness, and painful swelling of one or more salivary glands. The fever, usually of low grade, lasted for about two days. Glandular swelling persisted for 7 to 10 days. Other manifestations of mumps occurred most often in persons past the age of puberty. They included orchitis, incidence 25 to 35%; meningoencephalitis, 2 to 4%; oophoritis about 5%, and pancreatitis, myocarditis, presternal edema, and mastitis, occasionally seen.

Mumps orchitis was described as the most consistent clinical entity. Orchitis most often began one to eight days after the appearance of parotitis and was usually accompanied by a chill, a temperature of 102 to 104 F., testicular pain, vomiting, and often prostration. The day of onset was usually determined by history but sometimes by observation. In a study of 2,500 cases of mumps, Eagles [19] found the average duration of fever with orchitis to be 3.66 days, with a range from none to 9 days. High fever almost invariably accompanied the orchitis. McGuinness and Gall,[20] in a review of 1,378 cases of mumps, reported the average duration of fever with orchitis to be 4.2 days. A fever distribution curve for 492 of their cases showed that approximately 60% of the patients had fever from three to five days and 80% had fever for three days or longer.

Seventy-two case records of patients with mumps admitted to this hospital between 1948 and 1952 were reviewed in order that we might compare the clinical features with those described in the literature. The incidence of orchitis was higher than the general average, probably because only the more severely ill patients were admitted to the hospital. Forty-five patients, or 62.5%, had orchitis during their hospital course. The history of onset of orchitis was readily obtained and was considered reliable for those with testicular symptoms and fever. The duration of the febrile course of orchitis was about the same as that described in other series. The average duration of fever in 16 patients with orchitis receiving only symptomatic therapy was found to be 4.2 days, with a range from 2 to 8 days. Ten patients, or 62.5%, had fever from three to five days. Fifteen of the sixteen patients had fever for three days or longer, only one patient having fever for less than three days. The remaining 29 of the 45 orchitis patients received one or several antibiotics and had fever for an average of 4.5 days. The duration of testicular symptoms, tenderness, and swelling, was found to range from 6 to 21 days, with an average of 11 days. The latter observations were found to be less regularly recorded in the charts and

19. Eagles, A. Y.: Analysis of a 4 Year Epidemic of Mumps, Arch. Int. Med. **80**:374-387, 1947.

20. McGuinness, A. C., and Gall, E. A.: Mumps at Army Camps in 1943, War Med. **5**:95-104, 1944.

more difficult to evaluate because of the subjective nature of the complaint of tenderness and because of the lack of recognized standards of testicle size.

Therapy of patients having mumps with orchitis was then undertaken. All but one of the patients in the study were seen within 48 hours after onset of orchitis.

It was expected that an early decision could be reached after treating a very few patients, provided the therapeutic agent had no effect and the patients had the normal course of a total of three days of fever or longer.

Of six patients with mumps orchitis, four were treated with aureomycin, one with chloramphenicol, and one with oxytetracycline, as shown in the accompanying charts and in the following case reports.

## REPORT OF CASES

CASE 1.—E. J., a Negro aged 24, a truck driver, was admitted March 14, 1949, and discharged March 31.

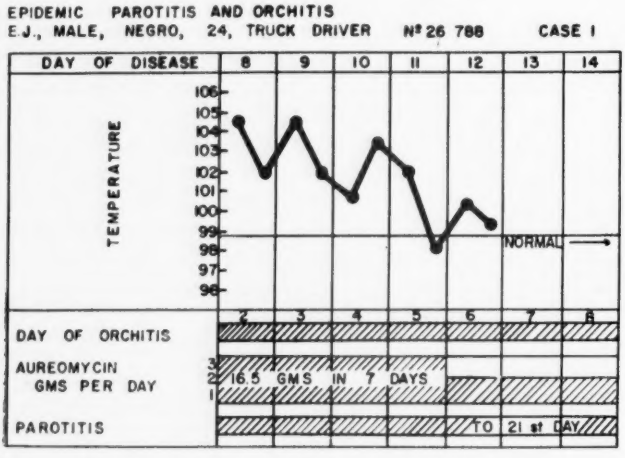


Chart 1 (Case 1).—Clinical record of patient treated with aureomycin.

Fever and bilateral parotitis were noted seven days before admission; submaxillary-gland swelling was noted for three days before admission; right testicular pain and swelling were noted one day before hospital admission. Rhinitis preceded the onset by 10 days. Marked cough and headache appeared three days before hospital admission.

At physical examination the patient was acutely ill, with a temperature of 104.4 F., a pulse rate of 100 beats a minute, enlargement of both parotid and submaxillary glands, and moderate swelling of both testicles and epididymes.

Laboratory examinations showed the white blood cell count, red blood cell count, sedimentation rate, and urine to be normal. Serologic tests for syphilis and the blood culture were negative. The complement-fixation test for mumps was positive in a dilution of 1 to 64 on the eighth day of illness. A roentgenogram of the thorax showed bilateral peribronchial infiltration.

*Course and Therapy.*—Therapy with aureomycin was begun on the eighth day of illness and the second day of orchitis. A total of 16.5 gm. of aureomycin was administered in seven days without apparent therapeutic effect. The patient's temperature became normal on the fourth day after treatment was begun. Testicular and salivary-gland swelling disappeared completely in two weeks.

CASE 2.—L. B., a Negro aged 28, a janitor, was admitted April 21, 1952, and discharged May 1.

Bilateral parotid swelling began four days before admission, and one day before admission the left testicle became painful and swollen. Two of the patient's children were ill with mumps.

Physical examinations showed a normal temperature and pulse on admission. Both parotid glands were moderately swollen, and the left testicle was tender, though not swollen.

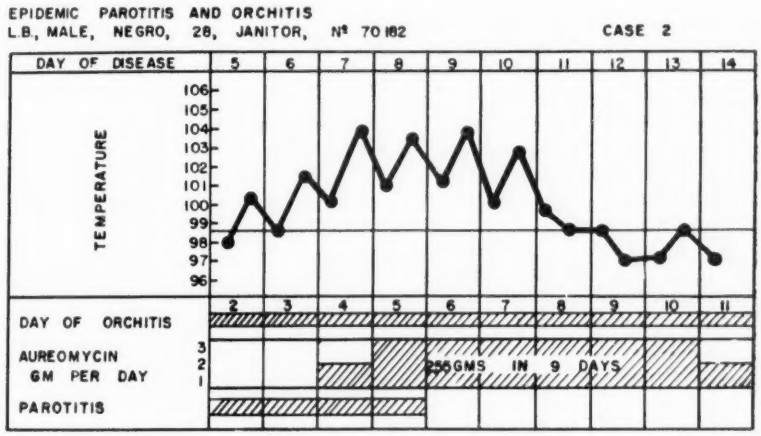
EPIDEMIC PAROTITIS AND ORCHITIS
L.B., MALE, NEGRO, 28, JANITOR, Nº 70 182
CASE 2
DAY OF DISEASE
5 6 7 8 9 10 11 12 13 14
TEMPERATURE
106 105 104 103 102 101 100 99 98 97 96
2 3 4 5 6 7 8 9 10 11
DAY OF ORCHITIS
AUREOMYCIN GM PER DAY
3 2 1
25.5 GMS IN 9 DAYS
PAROTITIS

Chart 2 (Case 2).—Clinical record of patient treated with aureomycin.

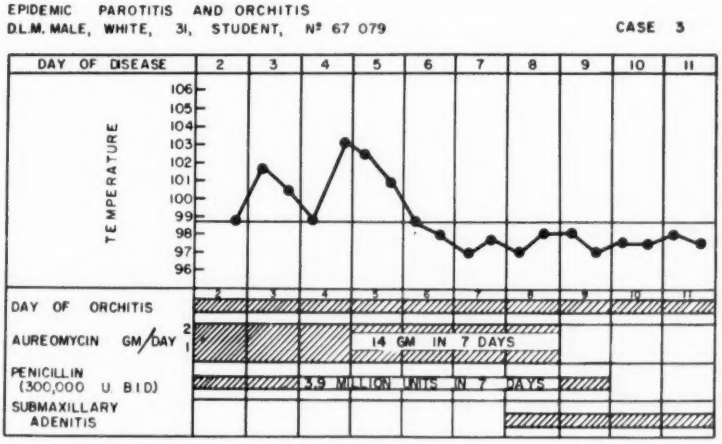
EPIDEMIC PAROTITIS AND ORCHITIS
D.L.M. MALE, WHITE, 31, STUDENT, Nº 67 079
CASE 3
DAY OF DISEASE
2 3 4 5 6 7 8 9 10 11
TEMPERATURE
106 105 104 103 102 101 100 99 98 97 96
DAY OF ORCHITIS
AUREOMYCIN GM/DAY
2 1
14 GM IN 7 DAYS
PENICILLIN (300,000 U BID)
3.9 MILLION UNITS IN 7 DAYS
SUBMAXILLARY ADENITIS

Chart 3 (Case 3).—Clinical record of patient treated with aureomycin and penicillin.

Laboratory examination showed the red blood cell count, white blood cell count, and urine to be normal. A serologic test for syphilis was negative. Complete examination of the cerebrospinal fluid was negative. Complement-fixation tests for mumps were positive in a dilution of 1 to 8 on the 4th day of disease and in a dilution of 1 to 64 on the 11th day of disease.

*Course and Therapy.*—The left testicle became swollen and tender after admission to the hospital. Administration of aureomycin was begun on the seventh day of illness and the fourth day of orchitis and was continued for nine days, the total dose being 25.5 gm., without apparent

therapeutic effect. The temperature became normal on the 12th day of disease and the 9th day of orchitis, which was five days after the beginning of aureomycin therapy. Parotitis and orchitis subsided by the 13th day of disease.

CASE 3.—D. L. M., a white student aged 31, was admitted Feb. 1, 1952, and discharged Feb. 12.

Pain in the right testicle began 24 hours prior to admission. There was no history of exposure to mumps.

Physical examination showed a temperature of 100 F. The right testicle was swollen and tender. No salivary-gland involvement was present at the time of admission to the hospital.

Laboratory examinations showed the red blood cell count, white blood cell count, and urine to be normal and a serologic test for syphilis to be within normal limits. The complement-fixation test for mumps was positive in a dilution of 1 to 256 on the 10th day of disease.

*Course and Therapy.*—Administration of aureomycin (total dose 14 gm.) and penicillin (total dose 3,900,000 units) was begun on the second day of illness and the second day of orchitis and continued for seven days without apparent effect. The temperature became normal on the sixth

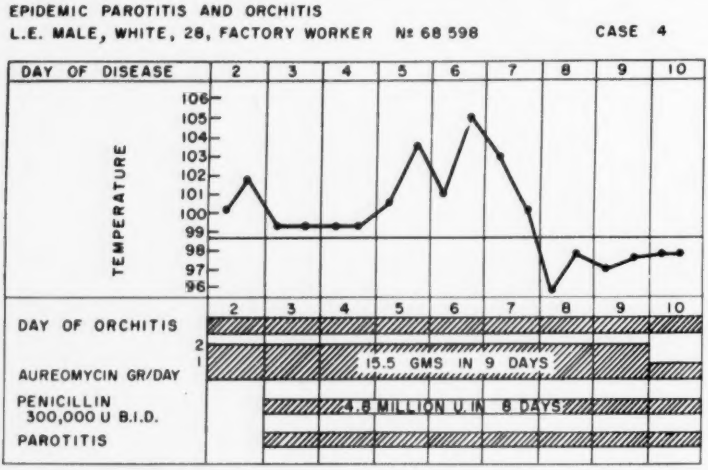
EPIDEMIC PAROTITIS AND ORCHITIS
L.E. MALE, WHITE, 28, FACTORY WORKER № 68 598
CASE 4
DAY OF DISEASE
2 3 4 5 6 7 8 9 10
TEMPERATURE
106 105 104 103 102 101 100 99 98 97 96
DAY OF ORCHITIS
2 3 4 5 6 7 8 9 10
AUREOMYCIN GR/DAY
2
1
15.5 GMS IN 9 DAYS
PENICILLIN 300,000 U B.I.D.
4.8 MILLION U. IN 8 DAYS
PAROTITIS

Chart 4 (Case 4).—Clinical record of patient treated with aureomycin and penicillin.

day of illness, four days after the beginning of treatment. On the eighth day of illness swelling and tenderness of the submaxillary glands appeared. By the 12th day of illness orchitis and submaxillary involvement had completely subsided.

CASE 4.—L. E., a white factory worker aged 28, was admitted March 11, 1952, and discharged March 21.

On the day before admission pain developed in the right lower part of the abdomen and right testicle. There was no history of exposure to mumps.

Physical examination revealed a temperature of 101.6 F. Tenderness in the right testicle and along the right inguinal canal was noted. No salivary-gland involvement was noted at the time of admission.

Laboratory examinations showed that the red blood cell count, white blood cell count, and urine were normal and a serologic test for syphilis within normal limits. The complement-fixation test for mumps was not performed.

*Course and Therapy.*—Administration of aureomycin (total dose 15.5 gm.) was begun on the 2d day of illness and of penicillin (total dose 4,800,000 units) on the 3d day of illness and continued through the 10th day of illness without apparent effect on the course of the disease.

Parotitis developed on the third day of illness. The temperature became normal on the seventh day of illness, five days after therapy was begun. Parotid and testicular involvement persisted until the 10th day of disease.

CASE 5.—J. H. A., a white truck driver aged 27, was admitted May 12, 1949, and discharged May 20.

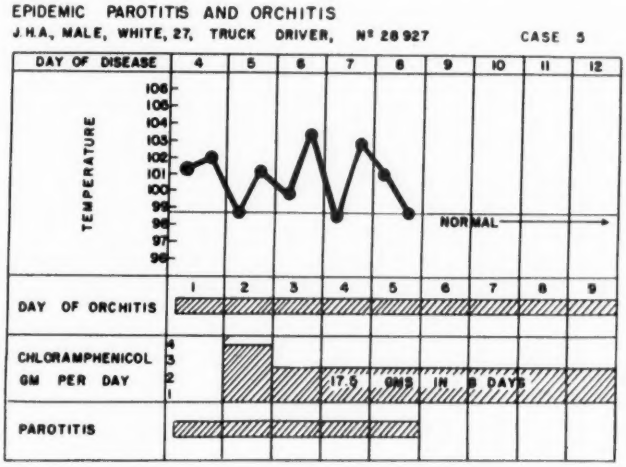
EPIDEMIC PAROTITIS AND ORCHITIS
J.H.A, MALE, WHITE, 27, TRUCK DRIVER, Nº 28 927
CASE 5
DAY OF DISEASE
4 5 6 7 8 9 10 11 12
TEMPERATURE
106 105 104 103 102 101 100 99 98 97 96
NORMAL
DAY OF ORCHITIS
1 2 3 4 5 6 7 8 9
CHLORAMPHENICOL GM PER DAY
4 3 2 1
17.5 GMS IN 8 DAYS
PAROTITIS

Chart 5 (Case 5).—Clinical record of patient treated with chloramphenicol.

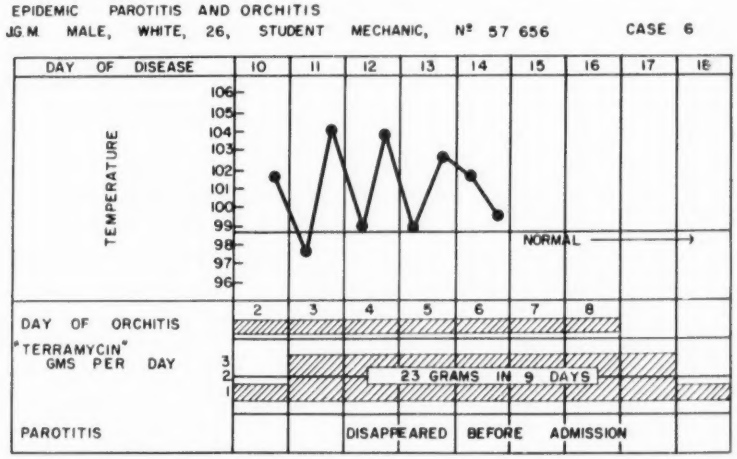
EPIDEMIC PAROTITIS AND ORCHITIS
J.G.M. MALE, WHITE, 26, STUDENT MECHANIC, Nº 57 656
CASE 6
DAY OF DISEASE
10 11 12 13 14 15 16 17 18
TEMPERATURE
106 105 104 103 102 101 100 99 98 97 96
NORMAL
DAY OF ORCHITIS
2 3 4 5 6 7 8
"TERRAMYCIN" GMS PER DAY
3 2 1
23 GRAMS IN 9 DAYS
PAROTITIS
DISAPPEARED BEFORE ADMISSION

Chart 6 (Case 6).—Clinical record of patient treated with oxytetracycline.

Painless swelling in the right parotid gland began three days before admission; painful swelling in the left parotid began two days before admission, and abdominal cramps and pains in the right testicle began eight hours before admission. Nausea, vomiting, and abdominal pain led to admission to a surgical service of the hospital. The patient stated that he was exposed to a case of epidemic parotitis two weeks before the onset of his illness.

Physical examination showed a temperature of 101.4 F. and a pulse rate of 96 beats a minute. There was slight pharyngeal erythema. Bilateral parotitis and right epididymo-orchitis were present.

Laboratory examinations showed the white blood cell count, the red blood cell count, and the urine to be normal. Serologic tests for syphilis were negative.

*Course and Therapy.*—Chloramphenicol was administered beginning on the fifth day of illness and the second day of orchitis. A total of 17.5 gm. was given in eight days without apparent therapeutic effect. Testicular swelling progressed gradually, and abdominal cramping and fever persisted until the eighth day of disease, the fifth of orchitis, three days after the beginning of therapy.

CASE 6.—J. G. M., a white student mechanic aged 26, was admitted June 7, 1951, and discharged June 20.

Swelling and pain in the right parotid gland began 10 days before admission, fever occurred and disappeared the next day, and testicular swelling began and fever recurred one day before admission.

Physical examination showed the temperature to be 101.6 F. and the pulse rate 110 beats a minute. Some tenderness was present over the right parotid gland but there was no parotid swelling. The left testicle was enlarged and was acutely tender.

Laboratory examinations showed the complete blood count and the urine to be normal, and serologic tests for syphilis were negative. A roentgenogram of the thorax showed a right paracardiac shadow, possibly due to a right-sided aortic arch.

*Course and Therapy.*—Oxytetracycline was administered orally, 23 gm. in nine days, beginning on the 10th day of illness and 2d day of orchitis, without apparent therapeutic effect. Diethylstilbestrol was also administered. The temperature became normal on the 15th day of illness and 7th day of orchitis, 4 days after the beginning of therapy. Parotid tenderness persisted only for a few days. Testicular swelling had subsided at the time of discharge.

In all six treated patients fever persisted for three days or more after administration of the antibiotic was begun. During the course of this study the course of the fever associated with orchitis was shorter in only one other patient treated similarly; namely, J. C. M. (No. 69,823), who was treated with oxytetracycline 24 hours after the onset of orchitis and whose temperature became normal 40 hours after treatment was begun. An occasional case of mumps orchitis of short duration such as this is to be expected and was not considered significant.

## COMMENT

Aureomycin, chloramphenicol, and oxytetracycline ("terramycin") had no favorable effect upon the symptoms of mumps orchitis, and the observations were considered sufficiently representative for us to conclude generally that the antibiotics were without effect in the treatment of mumps.

The choice of patients for treatment contributed largely to the significance of the result. The choice was based upon the reports of symptom analyses in the literature and observation of patients seen during the course of this study. Epidemic parotitis with orchitis tended to have a definite well-marked onset, with painful orchitis, fever, and often a shaking chill. The onset was recorded with a relatively high degree of reliability because it was distinctly recalled by the patient, who gave the history, and in some instances was observed by the physician, who was already treating the patient for parotitis. After such a definite onset, four out of five patients reported on in the literature and in the experience of this hospital then had a total of three or more days of a febrile course. It is fair to conclude that any regular alteration of the course of mumps orchitis by therapy would be readily recognized during the treatment of a small series of cases. The result was especially evident and required the smallest number of observed cases when, as in this study, the therapeutic agent had no effect upon the course of the disease. If the febrile course of

treated patients had proved to be shorter than the average of about four days, a greater number of patients would have had to be treated for us to observe the regularity of the favorable therapeutic effect.

No observations were made during the course of this study as to the reasons for the lack of therapeutic effect of aureomycin, chloramphenicol, and oxytetracycline in mumps orchitis. Since there is no evidence of direct action of these antibiotics upon the infectivity and multiplication of mumps virus in vitro, it is natural to assume that the lack of therapeutic effect is the result of an absence of any antivirus activity for the virus mumps. It is conceivable that the antibiotic effect of the three therapeutic agents would be prevented by the intracellular position of the mumps virus in cases of mumps orchitis, but this explanation, although it is frequently used to explain the lack of effect of antivirus agents in clinical disease, is less appropriate in this case than in most because aureomycin, chloramphenicol, and oxytetracycline do have clinical effects in diseases in which the eitological agent is found within the infected cells, namely, psittacosis, lymphogranuloma venereum, tularemia, and brucellosis. It is believed that the absence of therapeutic effect is consistent with the known facts about the experimental activities of these antibiotics upon the mumps virus.

## CONCLUSIONS

1. Epidemic parotitis and orchitis in adults observed in the first 24 to 36 hours after orchitis began was found sufficiently predictable in its course to serve as a test of antibiotic therapy.

2. Aureomycin, chloramphenicol, and oxytetracycline were not effective in altering the course of epidemic parotitis with orchitis.

# BRONCHIECTASIS

## A Bronchographic Study of Sixty Cases of Pneumonia

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AND
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BRONCHIECTASIS has been the subject of a vast literature. Nevertheless, despite the extensive investigation and bibliography, several aspects of the condition remain unsettled. Among these is the role of atelectasis in the pathogenesis of bronchiectasis. Another problem is the evolution of chronic, fixed bronchiectasis. Uncertainty as to the latter exists, perhaps, because most clinical investigations have been conducted on patients with established bronchiectasis. The evolution of their lesions could be inferred only retrospectively by history taking, pathological studies of surgical and autopsy specimens, and similar methods. Few reports were found concerning the development of the process from its inception. It was therefore decided to study the bronchi in consecutive cases of acute pneumonitis in young adult patients who had no history of previous pulmonary disease. From this investigation it was hoped that information might be obtained concerning (1) the occurrence of bronchial abnormalities, (2) their nature, (3) the course of patients showing bronchial involvement, and (4) the role of atelectasis in the formation of bronchiectasis.

### MATERIAL AND PROCEDURE

Sixty successive cases of pneumonitis in soldiers of average army age were selected. In each instance the diagnosis of pneumonia had been made and confirmed by clinical, laboratory, and x-ray means.

Our primary interest was the bronchial tree during acute pneumonitis in previously healthy lungs. All patients were excluded who gave a history of chronic pulmonary disease of any type, chronic cough, sinusitis, or frequent "head colds." At the time of admission to the ward, routine blood studies were performed and sputum was sent to the laboratory for typing and culture. In some cases in which typing and culture failed to reveal an accepted pathogen, an antistreptolysin titer was secured.

X-ray examination included the routine posteroanterior and lateral views. Oblique studies were made as indicated. Iodized oil (lipiodol®) was used for visualization of the bronchial tree after the acute febrile phase of the disease had subsided but usually while infiltrations were still seen roentgenographically. Initial bronchograms were made as early as one week, and up to eight weeks, after the onset of the pneumonia. It was deemed essential that complete filling of the bronchial branches to the lobe or lobes under study be obtained.

Bronchoscopy was done in 11 cases in which bronchograms showed bronchial abnormalities. Serial roentgenograms were obtained in all cases. When bronchial change was demonstrated, the patient was kept under observation in the hospital and serial laboratory, bronchoscopic, and bronchographic examinations were performed.

## FINDINGS

The 60 cases of pneumonia could be classified etiologically into five types: primary atypical, streptococcal (beta hemolytic), pneumococcal, bacterial (type undetermined), and bacterial or primary atypical pneumonia. The criteria for the classification of the cases and incidence of the various types are shown in Table 1. The comparatively high incidence of streptococcal pneumonias in this series may be due to the excellent streptococcal culture work of the hospital laboratory.[1]

It soon became apparent that no reliable, consistent roentgenographic distinction could be made between the cases of primary atypical pneumonia and those due to a virulent beta hemolytic Streptococcus. This observation has been noted by others.[2]

The age distribution of the patients was essentially the same as that throughout the entire army post. There was no significant age difference between the patients with and those without bronchial pathology.

The sites of pneumonic involvement were as follows: right lower lobe—25 cases; left lower lobe—24 cases; left upper lobe—5 cases; more than one lobe—6 cases. The location of involvement appeared unassociated with the frequency or severity of the atelectasis or bronchiectasis.

The principal symptom common to all cases was productive cough. Sputum varied between 50 and 200 c.c. in 24 hours. It was generally greenish and mucopurulent in appearance but never was observed to separate into discrete layers.

Physical examination of the chest yielded variable findings over the diseased areas, and the signs varied from day to day. When signs were present, they were usually fine or coarse moist rales at the site of the lesion, heard at the end of or throughout inspiration. The rales were generally accentuated by cough and deep inspiration.

The sedimentation rate was of interest in that elevation was a most unusual finding, even in those cases in which bronchoscopic examination revealed purulent material filling the bronchi.

The clinical courses of the pneumonic infections were classified into three grades of severity. Of the 60 cases, 37 were considered as mild, or Grade I, pneumonias; 18 were considered as moderately severe, or Grade II pneumonias, and 5 were considered as severe, or Grade III, pneumonias. Statistical analysis revealed no significant association between the severity of the pneumonia and the frequency or severity of bronchial disease as shown bronchographically.

Bronchoscopic studies were performed on 11 patients with bronchial abnormalities. Hyperemia of the mucosa in the branch bronchi leading to the area of pneumonitic involvement was noted in every case. Ten patients showed edema of the bronchial mucosa and seven a thick mucopurulent exudate in the lumen. In two patients a dry membranous exudate was present.

1. This work is under the supervision of Major Frederick S. Coombs Jr.

2. Hemolytic Streptococcus Pneumonia, Bull. U. S. Army M. Dept. **85**:88-91 (Feb.) 1945.

TABLE 1.—*Criteria for Etiological Classification of the Pneumonias*

| Type | Incidence | Specific Bacteriological Identification | Total Blood Leucocytes | Response to Sulfadiazine | Antistreptolysin Titer 1 to 7 Days After Onset | Clinical Severity | Comment |
|---|---|---|---|---|---|---|---|
| Primary atypical pneumonia..... | 30 (50%) | No | Usually under 12,000 | Poor | Normal | Variable, but tended to be mild | X-ray important in the diagnosis; chest signs clinically minimal or absent |
| Bacterial or primary atypical pneumonia ..... | 4 ( 7%) | No | Variable | Uncertain | Normal | Variable | Findings varied between primary atypical and bacterial pneumonia, and a definite decision could not be made |
| Bacterial pneumonia (type undetermined) ..... | 6 (10%) | No | Usually above 12,000 | Good | Normal | Variable, but tended to increased severity | Predominance of polymorphonuclear cells in the differential count; usually a history of chills; rales usually prominent |
| Beta hemolytic streptococcal pneumonia ..... | 16 (27%) | Yes | Variable | Good, but not as good as that in pneumococcal pneumonia | Elevated above 250 units | Variable to increased severity | Clinical and x-ray findings occasionally indistinguishable from those seen in primary atypical pneumonia |
| Pneumococcal pneumonia..... | 4 ( 7%) | Yes | Above 14,000 | Good | ..... | Variable to increased severity | Chills common; chest pain usually present; chest findings, classic "prune-juice" sputum |

The 11 patients were followed by serial bronchoscopic examinations. In 10 the bronchial mucosa assumed a normal appearance after a variable period. The mucosa of the 11th patient, who had shown no sign of recovery at 34 weeks after onset of disease, continued to present marked edema and hyperemia extending to the bifurcation. A large amount of mucopurulent secretions was observed coming from the diseased segment of lung.

All 60 patients showed roentgenographic evidence of segmental pneumonic involvement to a varying degree. Those with mild involvement showed small, faint or hazy, linear and/or patchy infiltrative densities. With more extensive disease, larger areas of involvement were observed, and the infiltrations were more opaque. In the patients with pneumococcal pneumonias, typical lobar and sublobar dense consolidations were found.

TABLE 2.—*Incidence of Atelectasis and Bronchial Abnormalities During the Course of Sixty Cases of Pneumonitis*

| | No. of Cases |
|---|---|
| I. Atelectasis | |
| A. Absent | 22 |
| B. Present | 38 |
| Lobar | 1 |
| Sublobar | 8 |
| Segmental | 29 |
| II. Bronchial abnormality * | |
| A. Absent | 35 |
| B. Present | 25 |
| Bronchiectasis | 8 |
| Mild bronchial abnormality | 17 |

* As demonstrated by bronchography.

Evidence of atelectasis was noted in the pneumonic infiltrations in 38 of the 60 cases (Table 2). These cases were subdivided into three main categories:

(*a*) Lobar collapse—one case. This patient showed massive collapse of the right lower lobe, which appeared homogeneously dense. Its upper border was concave upward and posteriorly. There were deviation of the mediastinum to the right, elevation of the diaphragm, narrowing of the rib interspaces, and depression of the right hilus (Fig. 10, *A* and *B*).

(*b*) Sublobar collapse—eight cases. There were homogeneous densities, of sublobar magnitude, with concave margins, and associated with several of the following: depression of the homolateral hilus, depression of the short fissure on the right side, mild shift of the mediastinum toward the same side, variable elevation of the diaphragm (Figs. 4*A*, 5*A*, and 8*A*).

(*c*) Segmental—29 cases. The most characteristic finding was a change in the course of the bronchopulmonary markings leading from the hilus to the involved area. The bronchi and vessels were observed to be displaced downward and inward instead of pursuing a more or less straight course into the lower lobes with normal branching and separation. As a result they took a distinctly curvilinear course, concavity of the branches being upward and outward (Fig. 2*A*). The infiltrations were seen along the course and at the distal ends of these curved bronchopulmonary markings. In addition, distinct crowding of the curved broncho-

pulmonary markings was noted. Not infrequently, associated horizontal plate-like focal atelectatic bands [3] were present at some time during the course of the pneumonic process. Occasionally, additional evidence of segmental collapse was noted, such as depression of the short fissure on the right side or of the homolateral hilus.

X-rays of the chest were made immediately prior to the bronchograms. In 12 instances atelectasis was observed to have persisted up to the time when the bronchograms were made. In each of these cases the bronchograms also demonstrated evidence of atelectasis, characterized by distinct crowding of the opacified bronchi and diminution in the size of the involved lobe or segment of lung. In several cases the sites of obstruction in the bronchi could be clearly demonstrated.

Complications were observed roentgenographically in 10 cases. Pleuritis, with varying amounts of effusion, was noted in nine cases. Of the latter, in one (beta hemolytic Streptococcus infection) an empyema and bronchopleural fistula developed. In a second case (beta hemolytic Streptococcus infection) pericarditis and a small pulmonary cavity developed in addition to the effusion. In the 10th case (primary atypical pneumonia) a pulmonary cavity developed during the course of the pneumonia and then disappeared spontaneously. The complications were observed with about the same frequency in the cases of primary atypical pneumonia and in the cases of bacterial pneumonia.

The roentgenographic findings in the bronchi following opaque-oil instillation varied considerably (Table 2). Since the terms employed in describing the findings will be used for the remainder of this paper, descriptive definitions are included, as follows:

1. Normal bronchi—35 cases. The bronchi tapered smoothly as they proceeded distally, subdivided, and ended in alveolar arborization. This peribronchiolar alveolar filling was considered essential for the diagnosis of a normal bronchus, as has been stressed by Ogilvie [4] and Fleischner.[5]

(*a*) Within the normally tapering bronchi in 29 of these 35 cases there was evidence of increased intraluminal secretion, characterized by small globular areas of radiolucency lying within the dense oil in the smaller bronchi. Differentiation from somewhat similar radiolucent areas due to incomplete filling and air pockets could be made with a fair degree of certainty.

(*b*) In six cases normally tapering bronchi were observed in which visualization ended abruptly at the distal ends owing to obstruction and about which no peribronchiolar filling was noted.

2. Mild bronchial abnormality—17 cases. This term has been employed for those cases in which the bronchi showed failure of normal peripheral tapering or slight dilatation and "beading," but in which considerable dilatation was not present. Obstruction, incomplete filling, and absence of peribronchiolar alveolar filling were always found associated. This status has been described by others as mild bronchiectasis (Figs. 3*B* and 4*B*).

3. Fleischner, F. G.; Hampton, A. O., and Castleman, B.: Linear Shadows in the Lung, Am. J. Roentgenol. **46**:610-618 (Nov.) 1941.

4. Ogilvie, A. G.: The Natural History of Bronchiectasis, Arch. Int. Med. **68**:395-466 (Sept.) 1941.

5. Fleischner, F. G.: The Pathogenesis of Bronchiectasis, Radiology **53**:818-833 (Dec.) 1949.

3. Bronchiectasis—eight cases. In these cases there was considerable widening of the bronchi. It should be noted that, as here applied, this is distinctly a radiographic anatomic term. It does not refer to the clinical status of the patient, the persistence or "reversal" of the dilatation, or the eventual prognosis of the case. Bronchial obstruction and absence of alveolar filling were present in every case and were considered a characteristic part of the picture of bronchiectasis (Figs. 5 *B* and 5 *C*, and 9 *B* and 9 *C*).

4. "Bronchopathy." This term will be used to include the cases of bronchiectasis and milder bronchial abnormalities.

In Table 3 the association of etiology of the pneumonia, presence of atelectasis, and occurrence of bronchial abnormality are recorded. It may be seen that atelectasis and bronchopathy occurred in each of the etiological subdivisions except that of pneumococcal pneumonia. In none of the four cases of the latter was atelectasis or bronchial abnormality noted.

The occurrence of atelectasis was significantly higher in streptococcal pneumonia (14 of 16 cases, or 87.5%) than in primary atypical pneumonia (16 of 30, or

TABLE 3.—*Etiology of the Pneumonia and Incidence of Atelectasis and Bronchopathy*

| Etiology of the Pneumonia | Atelectasis Present | | No Atelectasis | |
|---|---|---|---|---|
| | With Bronchopathy | No Bronchopathy | With Bronchopathy | No Bronchopathy |
| Primary atypical pneumonia | 7 | 9 | 2 | 12 |
| Beta hemolytic Streptococcus pneumonia | 12 | 2 | 1 | 1 |
| Bacterial pneumonia | 1 | 3 | 0 | 2 |
| Bacterial or primary atypical pneumonia | 2 | 2 | 0 | 0 |
| Pneumococcal pneumonia | 0 | 0 | 0 | 4 |
| | 22 | 16 | 3 | 19 |
| | 38 | | 22 | |

53.3%).[6] It may also be noted that among the atelectatic cases, bronchopathy occurred in a significantly higher percentage of those due to streptococcal infection (12 of 14, or 85.7%) than of those due to primary atypical pneumonia (7 of 16, or 43.7%).[7] The findings suggest that atelectasis and bronchial abnormality occur to a distinctly greater extent in streptococcal infections of the lung than in primary atypical pneumonia. However, primary atypical pneumonia does cause bronchial abnormality in a considerable percentage of cases.

The high correlation of atelectatic pneumonias and bronchographic abnormalities as demonstrated early in the study of these cases (Table 4) made it evident that a considerable association existed between atelectasis and bronchopathy.[8]

It is well recognized, however, that statistical association does not necessarily imply a direct etiological relationship. The data, therefore, were analyzed further in an attempt to determine whether atelectasis played a causal role in the establish-

6. The observed difference is 2.38 standard errors of the difference.

7. The observed difference is 2.91 standard errors of the difference.

8. Chi-square value is 10.73, giving a probability of less than 0.01 that such a distribution as seen in Table 4 could occur purely by chance. This finding indicates a statistically significant correlation.

ment of bronchial dilatation. The findings appeared to indicate that atelectasis was not necessary for the occurrence of bronchial dilatation. The evidence may be listed as follows:

(*a*) There was no consistent relation between degree of atelectasis and occurrence of bronchiectasis. Thus, one patient with lobar atelectasis and two of eight patients with sublobar atelectasis showed no bronchopathy.

(*b*) Three patients with no demonstrable atelectasis on the original pneumonic infiltration showed mild but definite bronchial abnormalities in bronchograms (Table 3).

(*c*) In 20 of the 29 patients with segmental atelectasis the lung reexpanded before the bronchogram was made. Nevertheless, bronchial dilatation was noted in 7 of these 20.

(*d*) Six patients showed obstruction of very small bronchi and absence of peribronchiolar alveolar filling (and therefore subbronchiolar alveolar atelectasis). Nevertheless, in these six patients, the involved bronchioles were of normal size and tapered normally to the points of obstruction.

TABLE 4.—*Association of Atelectasis and Bronchial Abnormality*

| | Atelectasis | |
|---|---|---|
| | Present | Absent |
| Bronchial abnormality | | |
| Present | 22 | 3 |
| Absent | 16 | 19 |

(*e*) It can be seen from Table 3 that atelectasis occurred in 16 cases of primary atypical pneumonia and in 14 cases of beta hemolytic streptococcal pneumonia. However, bronchial abnormality was observed in only 7 of the 16 cases of atelectatic primary atypical pneumonia, as against its presence in 12 of the 14 cases of atelectatic streptococcal pneumonias. This difference appears reasonably significant statistically [9] and would indicate that the bacterial etiology was more significant than the presence of atelectasis for the occurrence of bronchial dilatation.

In the patients showing persisting atelectatic pneumonia at the time of bronchography, the sites of obstruction could usually be visualized with the opaque oil. In the 29 patients with segmental atelectasis, the greater proportion (19) showed obstruction in the bronchial branches of the third and fourth order. In the group with sublobar involvement the obstruction was noted either in the branches of the first and second order or involved a large number of branches of the third order. In six patients without demonstrable atelectasis, obstruction was noted in one or two small fourth-order bronchial branches. In many patients, both with and without atelectasis, intraluminal secretion could be observed in the smaller bronchi.

Follow-up examinations were performed on 16 of the 25 patients who showed bronchial abnormalities in the initial bronchograms. The marked tendency of the bronchial abnormalities which appeared during the pneumonias to reverse to normal

9. Calculated chi-square value is 5.2 for $n = 1$, giving a probability of only 0.02 that such a difference might occur purely by chance.

is clearly evident from Table 5. Of the 16 patients with bronchopathy, the status of 11 reverted to normal. Five patients showed residual abnormalities at the time of the final bronchography, and in four of these five improvement of the original status was observed. Only one patient showed progressive bronchiectatic changes during the course of observation.

A distinct difference was noted between the patients with mild bronchial abnormalities and those with more marked bronchiectasis. Of the nine patients with the former who were followed, the status of six reversed to normal by two months. Two others took a longer period for complete reversal. Only one patient, although improved, still showed an abnormality at the time of the last examination (after four months). In contrast, of the seven patients with bronchiectasis, the status of three reversed in 3 to 4 months, and that of three failed to reverse completely during the period of observation (up to 10 months). In the seventh case (Patient 45) an initial moderate tubular bronchiectasis reverted to normal by the sixth week. A routine reexamination at four months showed a recurrence of mild bronchial abnormality in the bronchi previously involved. It would thus appear that generally (but subject to exception), the more marked the bronchopathy at the original observation, the longer the time for reversal and the greater the

TABLE 5.—*Course of the Patients Who Showed Bronchial Abnormalities on Initial Bronchogram*

| Type of Bronchial Abnormality First Shown | Total No. of Patients | No. Followed | No. Showing Complete Reversal to Normal | Time After Onset of Pneumonia for Reversal of Bronchi to Normal, Mo. | | | | | | | | Still Abnormal |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | |
| Mild bronchial abnormality.. | 17 | 9 | 8 | 1 | 5 | .. | .. | .. | 1 | .. | 1 | 1 |
| Bronchiectasis ..... | 8 | 7 | 3 | .. | 1* | 2 | 1 | .. | .. | .. | .. | 4* |

* Patient 45 showed moderate tubular bronchiectasis which disappeared by the sixth week. A follow-up bronchogram at the fourth month showed a recurrence of bronchial abnormality in the same region. The status of this patient therefore has been counted as a "reversal at two months" and "still abnormal."

probability of permanent disease. Further, if complete reversal is to occur, it is more likely to occur within four months. In only 2 of the 11 patients with bronchopathy whose status reversed did it do so after the fourth month.

## ILLUSTRATIVE CASES

1. *Nonatelectatic Segmental Pneumonia with Normal Bronchogram.*—CASE 1 (Patient 23).—C. L. P., a white man aged 33, was admitted to the hospital with a history of moderately productive cough and slight fever. The past history included no significant illnesses. Physical signs were minimal. An x-ray of the chest (Fig. 1*A*) revealed a patchy, nonatelectatic, segmental pneumonitis in the left lower lobe. The patient improved rapidly, and by three and one-half weeks after the onset of the illness (as determined by the history) there was complete disappearance of the symptoms, signs, and roentgenographic abnormalities. Bronchography at this time revealed a normal bronchial tree in the left lower lobe (Fig. 1*B*).

2. *Atelectatic Pneumonia with Normal Bronchogram.*—CASE 1 (Patient 48).—C. M. C., a white man aged 21, was admitted to the hospital with a history of cough, mucopurulent sputum, and mild right-chest pain of several days' duration. Fine rales were heard at the right base. A roentgenogram of the chest (Fig. 2*A*) showed a moderately atelectatic pneumonia in the right lower lobe. There was rapid improvement under routine symptomatic treatment. Two weeks after the onset of the illness the symptoms, signs, and abnormal x-ray findings had disappeared. Bronchography at this time revealed a normal bronchial tree in the right lower lobe (Fig. 2*B*).

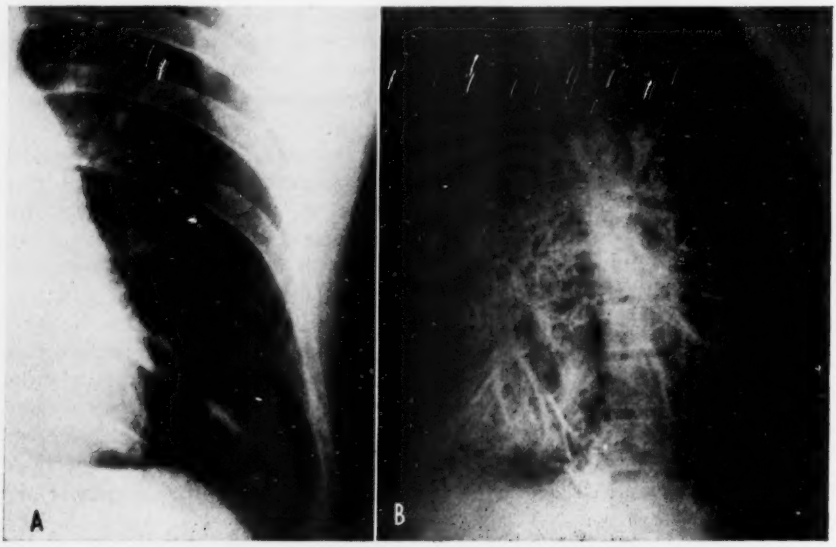



Fig. 1 (Case 1).—*A*, patchy, nonatelectatic, segmental pneumonitis in the left lower lobe. *B*, a normal bronchogram made immediately after the pneumonitis.

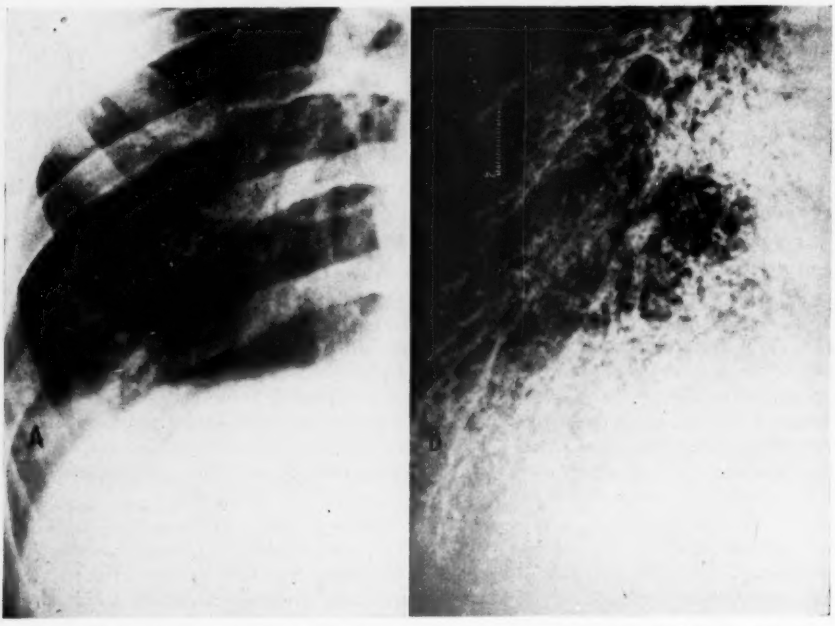



Fig. 2 (Case 2).—*A*, segmental, patchy atelectatic pneumonitis at the right base. Note the concave-upward superior margin of the infiltration. *B*, normal bronchogram made immediately after the pneumonitis.

3. *Nonatelectatic Pneumonia with Mild Bronchial Abnormality and Reversal.*—CASE 3 (Patient 35).—H. E. S., a white man aged 24, was admitted to the hospital with a pneumonia at the left base. An admission roentgenogram (Fig. 3*A*) showed a segmental infiltration in the left lower lobe with no atelectatic element. At two weeks after the onset of illness there were persisting signs and abnormal roentgenographic findings in the left lower lobe. Bronchoscopy at this time showed moderate hyperemia and edema of the mucosa of the left-lower-lobe bronchi.

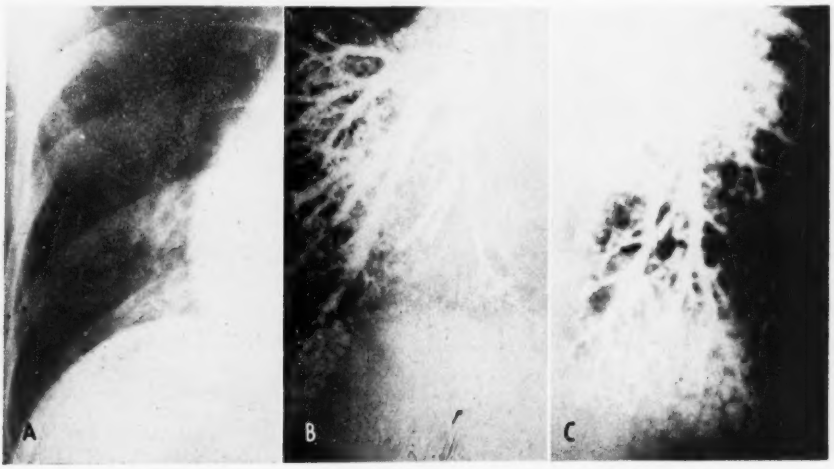



Fig. 3 (Case 3).—*A*, segmental, patchy, nonatelectatic pneumonitis in the left lower lobe. *B*, a bronchogram showing mild bronchial abnormalities. Note the slight dilatation, obstruction of smaller bronchi, and failure of peribronchial alveolar filling about the involved bronchi. *C*, a bronchogram made six weeks after *B*, showing a complete return to normal.

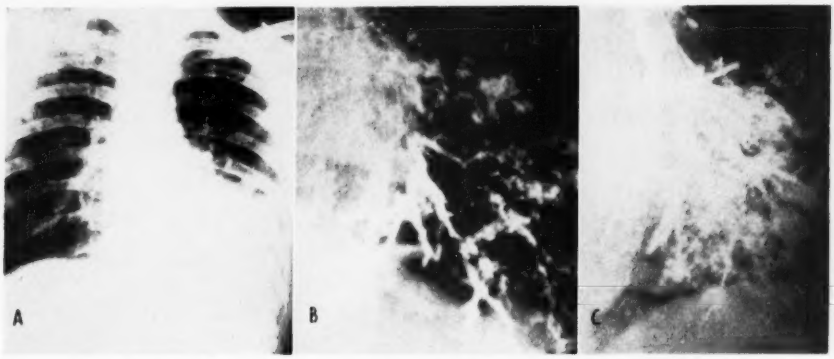



Fig. 4 (Case).—*A*, atelectatic, sublobar, dense consolidation in the left lower lobe. Note the concave-upward superior margin of the infiltration. *B*, a bronchogram showing somewhat more marked abnormalities in the branches of the left lower lobe bronchus. The findings could be considered mild tubular bronchiectasis. *C*, a bronchogram made six weeks after *B*, showing marked improvement. One bronchial branch still appears involved.

Bronchography (Fig. 3*B*) revealed mild bronchial abnormalities of the left-lower-lobe bronchial branches. The patient improved under observation. By eight weeks after the onset of illness all symptoms, signs, and abnormal x-ray findings had disappeared. Bronchoscopy at this time showed no significant abnormalities. Bronchography (Fig. 3*C*) also showed a complete return to normal.

4. *Atelectatic Pneumonia with More Marked Bronchial Abnormalities and Almost Complete Reversal.*—CASE 4 (Patient 60).—M. S., a white man aged 21, was admitted to the hospital with marked symptoms, signs, and x-ray evidence (Fig. 4*A*) of an extensive, patchy, atelectatic pneumonia in the left lower lobe. Two weeks after the onset of illness abnormal roentgenographic findings were still present. Bronchography at this time (Fig. 4*B*) revealed moderately

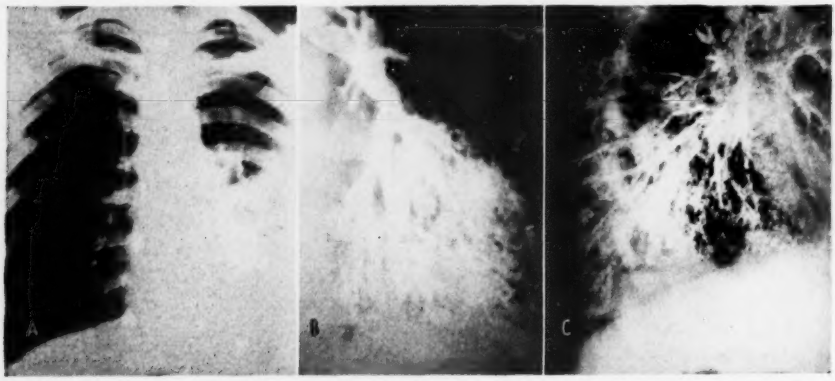


Fig. 5 (Case 5).—*A*, extensive atelectatic pneumonia in the left lower lobe. *B* and *C*, bronchograms made eight weeks after onset, showing definite bronchiectasis of the left lower lobe. *B*, frontal view; *C*, right anterior-oblique view.

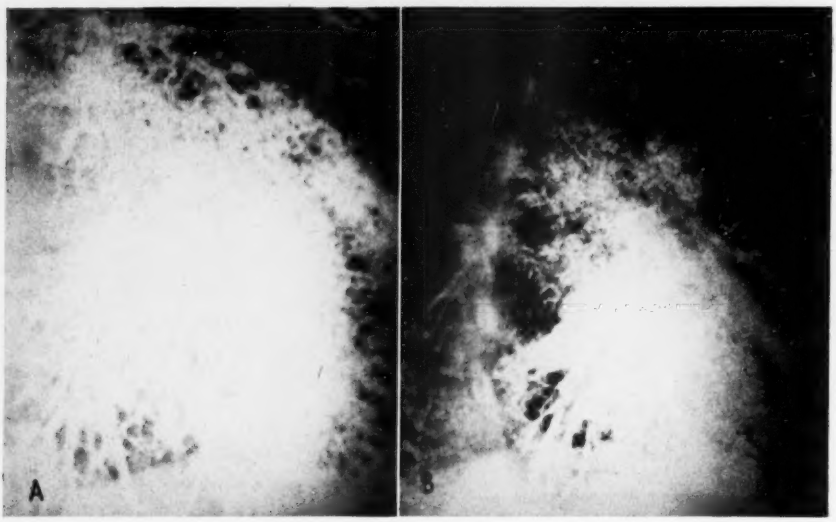


Fig. 6 (Case 5).—Normal bronchograms made five weeks after *B* and *C* in Figure 5. *A*, frontal view; *B*, right anterior-oblique view.

severe bronchial changes involving the branches of the left-lower-lobe bronchus. Mild crowding of these branches was present, indicating atelectasis. The patient was kept in the hospital, and he improved. By eight weeks, he was asymptomatic and the plain roentgenograms were normal. Repeat bronchography, however, revealed persisting bronchial abnormalities, although improvement had occurred (Fig. 4*C*). There was no longer evidence of atelectatic bronchial crowding.

A third bronchography was performed at 11 weeks and showed additional return of the smaller bronchi toward normal, but slight abnormalities were still present.

5. *Atelectatic Pneumonia with Bronchiectasis and Complete Reversal.*—CASE 5 (Patient 43).—N. D. M., a white youth aged 19, was admitted to the hospital with an extensive atelecta-

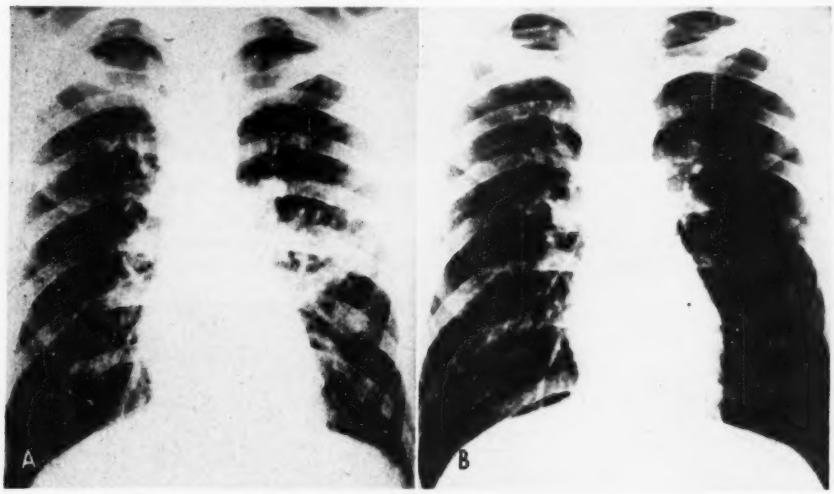



Fig. 7 (Case 6).—*A*, initial patchy, nonsegmental pneumonitis in the left lower lobe. *B*, complete clearing of the pneumonitis seen in *A*.

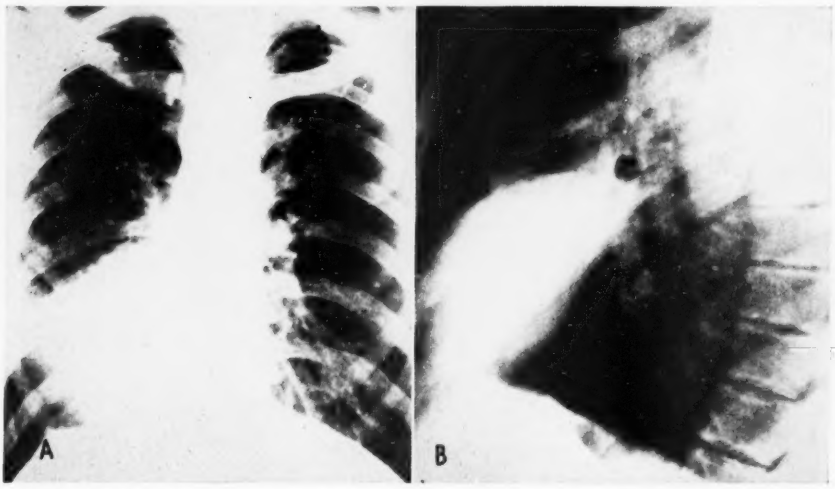



Fig. 8 (Case 6).—A second attack of dense atelectatic pneumonia in the lingula of the left upper lobe five months after the pneumonitis shown in Figure 7. *A*, frontal view; *B*, lateral view.

tic pneumonia in the left lower lobe (Fig. 5*A*) due to beta hemolytic Streptococcus Type A-19. The patient had a stormy course for the next month. There developed a pleural effusion, pericarditis, and pulmonary excavation, which were treated with penicillin given intramuscularly and intrapleurally. By the end of seven weeks there was marked improvement. The effusion,

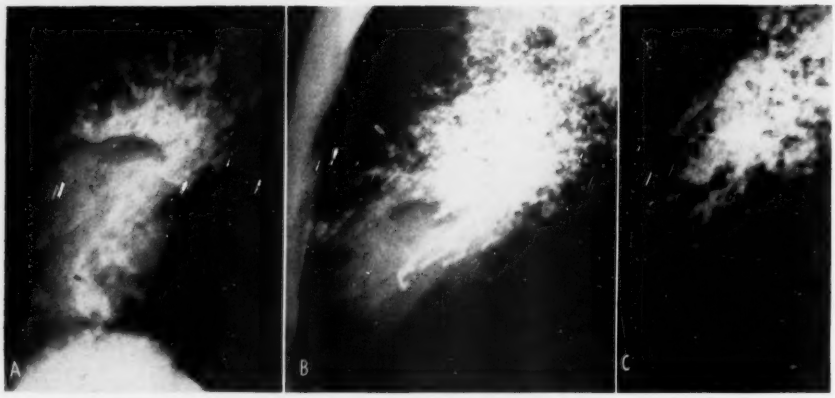



Fig. 9 (Case 6).—*A*, a lateral-view bronchogram made five weeks after the onset of the second attack. Note the complete obstruction of the lingular division of the left upper lobe bronchus. *B*, a lateral view made eight weeks after *A*, showing beginning filling of irregular, ragged, dilated branches of the lingular division. *C*, a lateral view made 21 weeks after *B*, showing slight further filling of markedly abnormal branches of the lingular division.

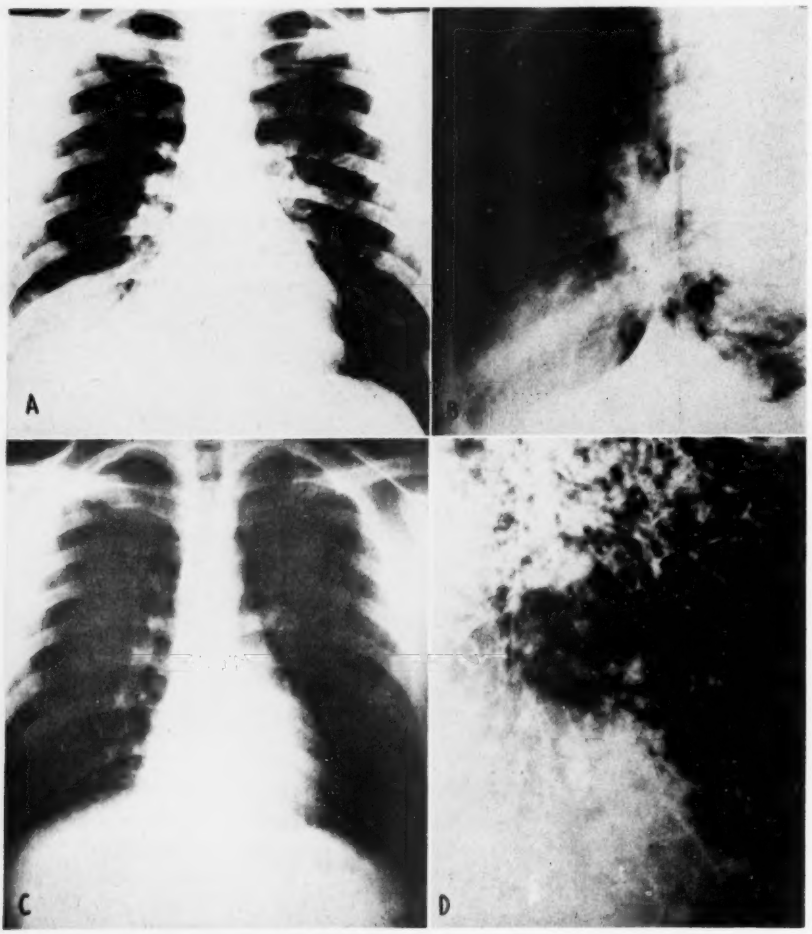



Fig. 10 (Case 7).—*A* and *B*, massive lobar atelectatic pneumonia of the right lower lobe. *A*, frontal view; *B*, lateral view, in which the concave-upward superior margins of the atelectatic consolidation are well demonstrated. *C*, complete clearing two weeks after the onset of illness. *D*, a normal bronchogram made at the same time as *C*.

pericarditis, and pulmonary excavation had disappeared. However, there were residual abnormal clinical and roentgenographic findings in the left lower lobe. Bronchography was performed at eight weeks. It showed definite bronchiectasis and atelectatic crowding of the left-lower-lobe bronchial branches (Fig. 5, *B* and *C*). The patient continued to improve, and by 13 weeks there were no clinical or roentgenographic abnormalities. A second bronchogram, at this time, showed complete reversal of the bronchi to normal and disappearance of the atelectasis (Fig. 6, *A* and *B*).

6. *Atelectatic Pneumonia with Bronchial Obstruction and Bronchiectasis, Irreversible.*—CASE 6 (Patient 24).—P. G. H., a white youth aged 19, was admitted to the hospital with pneumonia in the left chest anteriorly. He had been a patient at this hospital five months previously with a nonatelectatic primary atypical pneumonia in the left lower lobe posteriorly (Fig. 7*A*). This process cleared completely, and x-rays of the chest prior to discharge were normal (Fig. 7*B*). There was no history of other pulmonary disease. Admission roentgenograms revealed an extensive atelectatic pneumonia in the lingula and lower half of the left upper lobe anteriorly (Fig. 8, *A* and *B*). The local abnormal findings persisted unchanged, and bronchoscopy was performed at four weeks after the onset of the present illness. There were mild hyperemia and edema of the left main bronchus. A roentgenogram showed persisting atelectasis of the lingula of the left upper lobe. Bronchography at five weeks (Fig. 9*A*) showed complete obstruction and failure of filling of the lingular bronchus.

The patient was kept under observation in the hospital for 34 weeks. He had become afebrile and symptomatic except for a nonproductive cough. Serial bronchoscopies and bronchographies were performed at 13, 19, 27, and 34 weeks. The bronchoscopies revealed persisting edema and hyperemia of the left main bronchus. Mucopurulent secretion was observed coming from the left-upper-lobe ostium.

Bronchography at 13 weeks (Fig. 9*B*) showed additional shrinkage of the lingula. There was beginning filling of several of the main divisions of the lingular bronchus. These appeared irregular and dilated. At 27 and 34 weeks (Fig. 9*C*) there were progressive contraction of the lingula and visualization of additional segments of irregular, ragged, dilated bronchi in this segment.

7. *Lobar Atelectasis Followed by a Normal Bronchogram.*—CASE 7 (Patient 38).—R. T. C., a white man aged 19, was admitted to the hospital with mild symptoms and signs of a parenchymal process in the right lower lobe. Admission roentgenograms revealed a massive, lobar, atelectatic pneumonia in the right lower lobe (Fig. 10, *A* and *B*). The patient improved rapidly with symptomatic therapy. By two weeks after the onset of illness the patient was asymptomatic and the abnormal x-ray findings had completely disappeared (Fig. 10*C*). Bronchography revealed no abnormalities (Fig. 10*D*).

## COMMENT

The high incidence of bronchial disease following moderately serious pulmonary infections in patients without any history of previous pulmonary disease appeared to us to be of some significance. No similar observation was found in a rather careful review of the literature. Three main categories of information concerning the frequency of bronchiectasis were found. First, the occurrence of bronchial disease in pulmonary infections studied at autopsy was recorded.[10] Second, the incidence of a pneumonia history in patients with bronchiectasis was noted.[11]

10. Lisa, J. R., and Rosenblatt, M. B.: Bronchiectasis: Pathogenesis, Pathology and Treatment, New York, Oxford University Press, 1943, p. 127.

11. (*a*) Field, C. E.: Bronchiectasis in Childhood: I. Clinical Survey of 160 Cases, Pediatrics **4**:21-47 (July) 1949. (*b*) Raia, A.: Bronchiectasis in Children: With Special Reference to Prevention and Early Diagnosis, Am. J. Dis. Child. **56**:852-882 (Oct.) 1938. (*c*) McNeil, C.; MacGregor, A. R., and Alexander, W. A.: Studies of Pneumonia in Childhood: IV. Bronchiectasis and Fibrosis of the Lung, Arch. Dis. Child. **4**:170-189 (Aug.) 1929. (*d*) Findlay, L., and Graham, S.: Bronchiectasis in Childhood: Its Symptomatology, Course and Cause, ibid. **2**:71-96 (April) 1927. (*e*) Thorpe, E. S., Jr.: Chronic Bronchiectasis in Childhood, with Observations on Early Diagnosis, Am. J. M. Sc. **177**:769-767 (June 29) 1929.

Third, bronchiectasis occurring as a complication in large series of patients with pneumonia was listed.[12] In the series reported there was usually a selection of patients for bronchography, only those with residual parenchymal infiltrations being studied with opaque oil. It was felt, therefore, that the routine bronchography of 60 consecutive patients with pneumonia might give more accurate information as to the incidence of associated demonstrable bronchial disease. As might be expected, we observed bronchial abnormalities early in the course of the pneumonitis with greater frequency than was reported when selected patients had bronchograms only on the finding of residual pneumonitis. Thus, fully 25 of the 60 patients showed varying degrees of bronchopathy when studied early. In addition, a distinct difference in the incidence of bronchial abnormality was observed in the various etiological types of pneumonia. Streptococcal infections appeared most noxious to the bronchial tree. Of the 16 patients with streptococcal pneumonia, 13 showed bronchographic abnormalities. This high incidence of bronchial abnormalities in streptococcal pneumonias has been described elsewhere.[13] Less well known, but previously reported,[14] is the distinct tendency toward bronchopathy in primary atypical pneumonia. Our series showed early demonstrable bronchial abnormality in 9 of 30 such cases. Four patients with pneumococcus pneumonia without bronchopathy were observed. Others also have reported on the comparatively low incidence of bronchiectasis in pneumococcal lung infections.[15]

The necessity of atelectasis for the development of bronchiectasis is still a subject of controversy.[16] The high degree of association of the two conditions is commonly acknowledged and is well demonstrated in our own material. However, more detailed statistical analysis of our data and careful study of each individual

12. (*a*) Van Ravenswaay, A. C.; Erickson, G. C.; Reh, E. P.; Siekierski, J. M., and Gumbiner, B.: Clinical Aspects of Primary Atypical Pneumonia, J. A. M. A. **124**:1-6 (Jan. 1) 1944. (*b*) Karpel, S.; Waggoner, I. M., and McGowan, O. S.: Primary Atypical Pneumonia: A Critical Analysis of 500 Cases, Ann. Int. Med. **22**:408-418 (March) 1945. (*c*) Meakins, J. C.: The Practice of Medicine, Ed. 5, St. Louis, C. V. Mosby Company, 1950, pp. 247-248. (*d*) Cecil, R. L.: A Textbook of Medicine, Ed. 7, Philadelphia, W. B. Saunders Company, 1948, pp. 926-927. (*e*) Yater, W. M.: Fundamentals of Internal Medicine, Ed. 3, New York, Appleton-Century-Crofts, Inc., 1949, p. 315.

13. Thorpe.[11e] Raia.[11b] Landis, H. R. M.: Bronchiectasis, in Diseases of the Bronchi, in Nelson New Loose-Leaf Medicine, New York, Thos. Nelson & Sons, 1937, vol. III, p. 446.

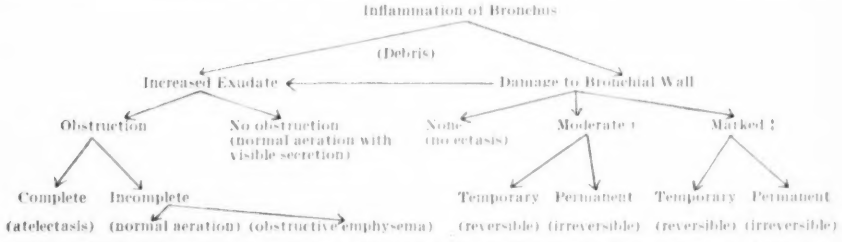
14. (*a*) Blades, B., and Dugan, D. J.: Pseudo Bronchiectasis Following Atypical Pneumonia, Bull. U. S. Army M. Dept. **70**:60-68 (Nov.) 1943. (*b*) Van Ravenswaay and others.[12a] (*c*) Karpel, Waggoner, and McGowan.[12b] (*d*) Kay, E. B.: Bronchiectasis Following Atypical Pneumonia, Arch. Int. Med. **75**:89-104 (Feb.) 1945.

15. Burrell, L. S. T.: Bronchiectasis, Bronchiolectasis and Bronchial Spirochaetosis, in British Encyclopaedia of Medical Practice, Vol. 2, London, Butterworth & Company, Ltd., 1936, p. 683. Thorpe.[11e] Meakins.[12c] Cecil.[12d]

16. (*a*) Ogilvie.[4] (*b*) Fleischner.[5] (*c*) Lander, F. P. L., and Davidson, M.: The Ætiology of Bronchiectasis (with Special Reference to Pulmonary Atelectasis), Brit. J. Radiol. **11**:65-89 (Feb.) 1938. (*d*) Jennings, G. H.: Re-Expansion of the Atelectatic Lower Lobe and Disappearance of Bronchiectasis, Brit. M. J. **2**:963-965 (Nov. 13) 1937. (*e*) Hammon, L.: Bronchiectasis, in Oxford Loose-Leaf Medicine, edited by H. A. Christian, B. Gordon, W. J. Kerr, and C. S. Sturgis, New York, Oxford University Press, 1949, Vol. 2, Chap. 1-A: Diseases of the Bronchi, pp. 24-28.

case, as described, make it apparent that the bronchial abnormalities can be ascribed in no logical manner to atelectasis. Indeed, the only theory which can apparently explain all the variations of sequence and coincidence of atelectasis and bronchiectasis requires the assumption of a third primary etiological factor which can cause atelectasis, bronchiectasis, or both. This third factor is inflammation of and injury to the bronchial wall by the noxious agent. Bronchial dilatation occurs as a result of damage to the neuromuscular apparatus present in the bronchial wall or from actual destruction of the bronchus in severe infections. Atelectasis appears only when the lumen of the involved bronchus becomes sufficiently plugged with inflammatory exudate and detritus to obstruct the airway to the distal bronchopulmonary segment. The obstruction probably augments the bronchial damage and dilatation but plays only a secondary role. Confirmatory evidence of this thesis is the finding of inflammatory changes in the bronchial walls of all 11 patients

TABLE 6.—*Clinical Variations Following Bronchial Infection**




* Words in parentheses represent clinical findings encountered. All combinations of the results of "Increased Exudate" and "Damage to Bronchial Wall" have been observed clinically.
† Mild bronchial abnormality.
‡ Bronchiectasis.

who had bronchoscopy. Each of these 11 patients also showed bronchial abnormalities on bronchography, 5 showing definite bronchiectasis and 6 showing milder bronchial abnormalities. Further, if the theory that bronchial-wall damage is the primary factor for the development of atelectasis and bronchiectasis is correct, then a chart of the possible combinations and permutations of these three elements should include all observed clinical variations. Such a chart is shown in Table 6, which in fact does include all the variations observed in our 60 cases. A similar chart constructed with atelectasis as the etiological factor is completely inadequate for the clinical variations encountered.

The primary significance of damage to the bronchial wall by infection and the etiological unimportance of atelectasis in bronchiectasis have been stressed by other observers.[17] However, it is felt that the independent arrival at the same conclusion purely from our own clinical data adds further evidence to the validity of this theory. It is of interest to note that essentially the same conclusions were reached

17. McNeil, MacGregor, and Alexander.[11e] Thorpe.[11e]

by Golden [18] and Lisa and Rosenblatt [19] on primarily pathological evidence and by Tannenberg and Pinner [20] after extensive experimental work on rabbits.

In the present series, 25 of the 60 patients showed definite bronchographic abnormalities when the studies were carried out comparatively early in the course of the pneumonia. There is no intended implication that the bronchial abnormalities persisted permanently or even for an extended period in the large majority of these patients. On the contrary, serial bronchograms at about monthly intervals most often showed marked improvement in the appearance of the abnormal bronchi. Indeed, the tendency of the bronchi toward rapid, spontaneous recovery appeared to be a significant finding in this study. As was stated, of the 16 patients with bronchial pathology who were followed, the status of 11 reversed by the fourth month. Tannenberg and Pinner [20] showed that in experimentally produced bronchiectasis the peak of induced bronchial pathology occurred about four weeks after infection. Thereafter the bronchi showed a considerable tendency toward recovery. The similarity of bronchial behavior in clinical and experimental (in rabbits) early bronchiectasis appears noteworthy, and the importance of early bronchiographic study becomes apparent. If initial bronchograms had been done late in the course of the pneumonias they might often have appeared normal. The actual sequence of frequent brochial abnormalities with a great tendency toward rapid spontaneous recovery would have been overlooked. It was also noted that at the time the initial bronchial abnormalities were observed, most of the patients had become afebrile and practically asymptomatic. Thus, the presence of fever or an elevated leucocyte count was not an accurate guide in foretelling the occurrence of demonstrable bronchial abnormalities.

How complete the reversal will be apparently depends upon the degree of damage to the neuromuscular apparatus and elastic tissue of the bronchial wall by the inflammatory process.[21] In mild cases, probably with simple cellular infiltration, the bronchi revert to normal quickly after recovery. In severe cases with actual destruction of the entire wall, the bronchi probably never become completely normal. Even in these, however, some improvement occurs. The degree of bronchial dilatation may be initially identical in the bronchiectatic cases in which reversal occurs and in those in which the bronchi do not become completely normal. This fact is shown in the case reports presented earlier in the paper. We believe both types must be classified as true early bronchiectasis and that a rather long period of observation may be necessary to determine whether the abnormality will be progressive, remain stationary, or show a return to normal status. Instances of reversible bronchiectasis have been reported with such increasing frequency [22] that

18. Golden, A.: Pathologic Anatomy of "Atypical Pneumonia, Etiology Undetermined": Acute Interstitial Pneumonitis, Arch. Path. **38**:187-202 (Oct.) 1944.

19. Lisa and Rosenblatt,[10] pp. 97-100.

20. Tannenberg, J., and Pinner, M.: Atelectasis and Bronchiectasis, J. Thoracic Surg. **11**:571-616 (Aug.) 1942.

21. Field.[11a] Ogilvie.[4] Kay.[14d] Hammon.[16e]

22. Field.[11a] Neuhof, H., and Thomas, A.: Acute Suppurative Bronchopneumonia, Arch. Int. Med. **75**:45-64 (Jan.) 1945. Kay.[14d] Ogilvie.[4] Fleischner, F. G.: Reversible Bronchiectasis, Am. J. Roentgenol. **46**:166-172 (Aug.) 1941. Blades and Dugan.[14a] Raia.[11b] Findlay and Graham.[11d] Jennings.[16d] Ochsner, A.: An Unappreciated Cause of Chronic Bronchitis, J. A. M. A. **93**:188-191 (July 20) 1929. Hammon, L.: Chronic Non-Tuberculous Basal Infections of the Lungs, Am. Rev. Tuberc. **40**:363-378 (Oct.) 1939.

they can no longer be considered as freakish medical rarities. By now they appear to warrant a recognized place in any classification of bronchiectasis and merit definite consideration in determination of the type of therapy for a given case. To label cases in which reversal occurs as "pseudobronchiectasis" [148] would seem misleading, since no bronchographic or definite clinical differences are present when the early bronchiectasis is first demonstrated. It would seem more accurate to use the term "bronchiectasis" generically, with such subdivisions as "recent" or "chronic," and "progressive," "stationary," or "retrogressive." Such a classification would express more clearly the dynamic aspect of the process. It is also possible that a patient might show a complete reversal to normal at one time and later exhibit a return of abnormality in the same bronchi. This sequence of events was observed in one of our patients. Indeed, none of our patients whose status reverted to normal were followed sufficiently long to permit any definite conclusion as to the permanency of the reversal.

Finally, a note concerning the bronchographic examination itself appears warranted. Detailed delineation of the small bronchioles and peribronchiolar alveolar filling was thought desirable in searching for bronchiolar abnormalities and plugging by exudate. It was therefore decided to employ a large amount of opaque oil to insure complete filling. From 10 to 20 cc. per lobe was usually employed, and as much as 40 to 50 cc. was instilled bilaterally in some cases. These amounts are considerably greater than that required in the usual case for the diagnosis of bronchiectasis and are not recommended in routine bronchography. During the early stages of the study there was considerable hesitation in placing such large amounts of opaque oil into a lung which was the site of still-active pneumonitis. We were naturally concerned about unfavorable complications from the procedure and would certainly have discontinued the investigation had any untoward event occurred. It soon became apparent, fortunately, that the opaque oil was innocuous. In only 2 of the 60 patients new small patches of pneumonitis appeared about 10 days after the bronchograms and quickly subsided. Even these patches may not have been due to the opaque oil, since successive attacks of pneumonitis are not unusual in primary atypical pneumonia. In no other cases did the opaque oil alter the course of the disease or retard rapid recovery of the patient. We were also agreeably surprised at the rapidity with which the contrast oil was expelled from the lungs. In no case was there a persistent "flooding" phenomenon of large opaque oil residuum at the time of the succeeding examination, about a month later. Not infrequently, only minute, almost unrecognizable, stippling was present after four weeks. Repeated bronchographic examination also did not noticeably impair the ability of the bronchi to expel the contrast oil. The final conclusion was that opaque oil, even in large and repeated doses, was essentially harmless to the lungs studied in this series and could be used without concern.

## SUMMARY

Early bronchographic studies were performed on 60 consecutive pneumonia patients who had no history of previous pulmonary disease.

Bronchial abnormalities were observed in 25 of the 60 patients.

The etiological agents of the pneumonias were studied and related to the occurrence of atelectasis and bronchial disease. Streptococcal pneumonias were

accompanied by significant bronchopathy in a large percentage of cases. The incidence of demonstrable bronchial abnormalities in primary atypical pneumonia was lower, but still of considerable magnitude.

Analysis of the material appeared to indicate that atelectasis does not cause bronchiectasis. Rather, both the atelectasis and the bronchiectasis resulted from a common factor, i. e. inflammatory injury to the bronchus.

Serial bronchograms of patients showing initial bronchial abnormalities were performed and demonstrated a great tendency for the abnormal bronchi to revert to normal. In practically all the patients with bronchiectasis the status reversed completely or improved considerably. The significance of reversible bronchiectasis in the understanding of bronchiectasis in general is discussed.

The safety of instilling comparatively large amounts of iodized oil (lipiodol®) early in the course of pneumonia for any such study is demonstrated.

829 Park Ave.

# KAPOSI'S SARCOMA ASSOCIATED WITH LYMPHOSARCOMA

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AND
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THERE is a tendency among contemporary writers to include Kaposi's multiple idiopathic hemorrhagic sarcoma in the lymphoblastoma group. Evidence in support of the relationship of Kaposi's sarcoma to the reticuloendothelial system is the increasing number of case reports of Kaposi's sarcoma coexisting with other members of the lymphoblastoma group. The following case report of Kaposi's sarcoma associated with lymphosarcoma is another example of the interrelationship of these diseases.

## REPORT OF A CASE

A 78-year-old Negro had been admitted to Cook County Hospital on several occasions because of lymphosarcoma of the lymph nodes. During May and June, 1950, he was treated with roentgen rays to the cervical, sternal, and abdominal areas. The lymph nodes gradually decreased in size, and his general health improved. At the time of his discharge seven months later, he had swelling of the penis and a few nodules at the base. In July, 1951, a "small bump" appeared on the right thigh. New papular lesions appeared adjacent to this lesion, and within two weeks the eruption covered the upper half of the anteromedial surface of the right thigh.

On examination there was an eruption of the anteromedial surface of the upper half of the right thigh which consisted of numerous nodules varying in size from 1 mm. to 2 cm. The nodules were reddish-brown to blue, and some were slightly indurated. This induration extended to the right inguinal area and fused with slightly enlarged inguinal lymph nodes. There was some hyperpigmentation of the skin of the involved area.

There was a diffuse swelling of the penis with a few small indurated papules at the base and hyperpigmentation of the overlying skin. Two hyperpigmented patches with central crusting were present above the left knee anteriorly. A moderately enlarged lymph node was present in the right axilla.

*Laboratory Examinations.*—The urine was normal. A hemogram showed 59% hemoglobin, with 3,070,000 red blood cells per cubic millimeter. There were 2,500 white blood cells per cubic millimeter, with 52% neutrophiles, 30% lymphocytes, and 16% monocytes. Blood chemistry determinations revealed 48 mg. of nonprotein nitrogen, 6.1 gm. of total proteins, 3.2 gm. of albumin, and 2.9 gm. of globulin per 100 ml.

*Sternal Marrow Examination.*—The marrow was moderately cellular. Megakaryocytes were present and appeared normal. The ratio of nucleated red blood cells to white blood cells was approximately 1:2. Erythropoiesis was normoblastic. Granulopoiesis revealed a moderate increase in eosinophiles. The results were compatible with a biopsy diagnosis of lymphoblastoma.

*Skin Biopsy.*—The diagnosis was Kaposi's hemorrhagic sarcoma.

*Lymph Node Biopsy.*—The diagnosis was lymphosarcoma.

From the Department of Dermatology, Northwestern University Medical School, Dr. Herbert Rattner, chairman, and Cook County Hospital, service of Dr. James R. Webster.

Fig. 1.—Nodules of Kaposi's sarcoma on the thigh.

Fig. 2.—Kaposi's sarcoma of the skin; low-power magnification.

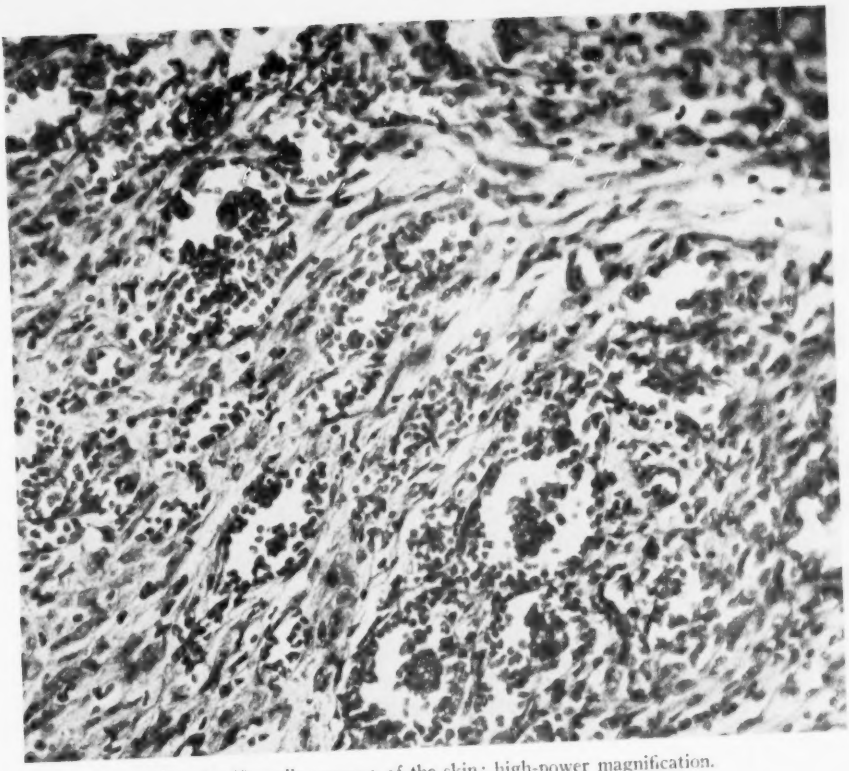

Fig. 3.—Kaposi's sarcoma of the skin; high-power magnification.

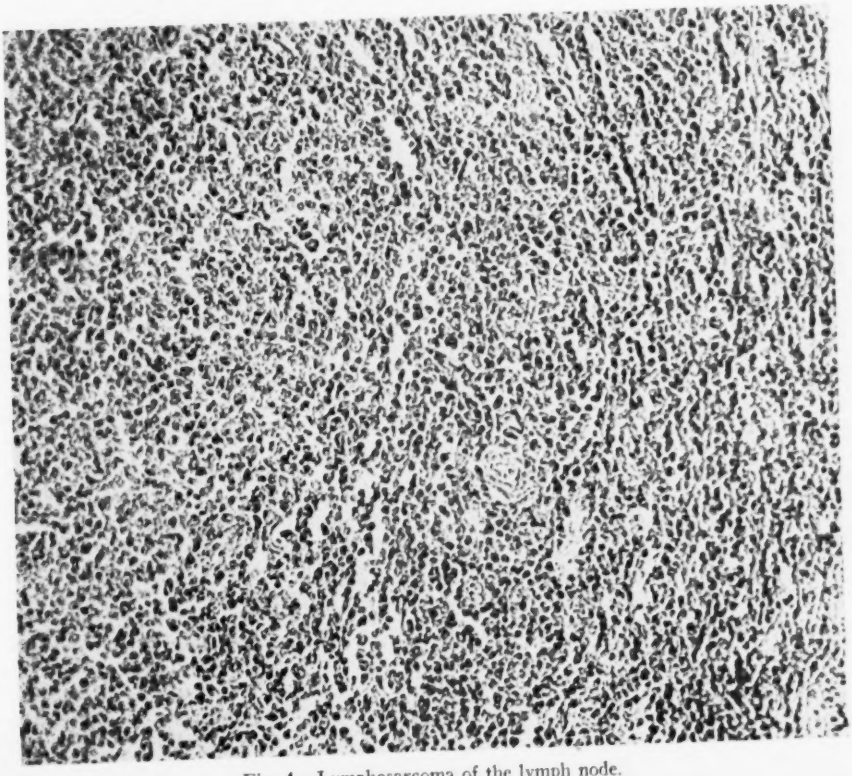

Fig. 4.—Lymphosarcoma of the lymph node.

REVIEW OF THE LITERATURE

Neither Kaposi's sarcoma nor lymphoblastoma is uncommon, yet few cases of their coexistence were reported in the older literature. Only in recent literature has an increasing incidence of the association of Kaposi's sarcoma and lymphoblastoma been reported.

*Mycosis Fungoides.*—Willis [1] suggested that Kaposi's sarcoma may be a variant of the lymphoblastomas with prominent skin lesions related to those of Hodgkin's disease and mycosis fungoides. In the case reported by Lane and Greenwood [2] Kaposi's sarcoma, confirmed microscopically, appeared late in the course of the mycosis fungoides. There was a typical history of mycosis fungoides of four years' duration. The disease passed through the prefungoid stage, and eventually typical tumors developed, for which extensive roentgen ray therapy was given. Then there appeared on the feet, small, round, dome-shaped, nonpigmented tumors which grew rapidly in size and number so that before death it was almost impossible to distinguish the toes. The tumors gradually extended up the leg. Earlier biopsies of a nodule had confirmed the diagnosis of mycosis fungoides. Histologic examination of these tumors showed changes typical of Kaposi's sarcoma, with considerably less pigmentation than is usually found. In addition, sections after death showed at one end of a nodule a picture of Kaposi's sarcoma and at the other end of the same slide the typical picture of mycosis fungoides. Lapowski [3] reported a case in which the lesions on the toes were Kaposi's sarcoma, while those on the trunk were mycosis fungoides.

*Hodgkin's Disease.*—A 65-year-old man, reported on by Goldschlag,[4] had been ill for four years with a disease characterized by enlargement of the liver, spleen, and lymph nodes; remittent fever; weight loss, and slight leucocytosis. A diagnosis of malignant lymphogranulomatosis was made. Three and one-half years after the onset of symptoms, pigmented raised nodules appeared on the lower extremities and the right side of the thorax. They exhibited the gross and microscopic characteristics of idiopathic hemorrhagic sarcoma of Kaposi. The author believed that the two diseases of the lymphatic system occurred presumably as the result of the same stimulus. The author discussed this case further in the *Australian Journal of Dermatology.*[4b]

Talbott [5] reported the case of a 56-year-old woman with Hodgkin's disease in whom superficial glandular enlargement was preceded by evidence of Kaposi's sarcoma of the skin. No change was observed in the skin lesions after one course of nitrogen mustard (methyl bis-[$\beta$-chloroethyl] amine hydrochloride) therapy. Significant regression of the superficial lymph nodes was not noted.

1. Willis, R. A.: The Pathology of Tumors, St. Louis, C. V. Mosby Company, 1948, p. 780.

2. Lane, C. G., and Greenwood, A. M.: Lymphoblastoma (Mycosis Fungoides) and Hemorrhagic Sarcoma of Kaposi in the Same Person, Arch. Dermat. & Syph. **27**:643 (April) 1933.

3. Lapowski, P.: Idiopathic Multiple Pigment Sarcoma (Kaposi), Arch. Dermat. & Syph. **33**:170 (Jan.) 1936.

4. (*a*) Goldschlag, F.: Über einen Fall von Sarcoma idiopathicum hemorrhagicum Kaposi mit ungewöhnlichem Vorstadium, Dermat. Wchnschr. **100**:204 (Feb.) 1935: (*b*) A Case of Sarcoma Idiopathicum Hemorrhagicum Kaposi, Australian J. Dermat. **1**:69 (March) 1951.

5. Talbott, J. H.: Clinical Manifestations of Hodgkin's Disease, New York J. Med. **47**:1883 (Sept. 1) 1947.

The patient reported on by Greenstein and Conston [6] was a 54-year-old white man who was first seen because of weight loss and weakness. Physical examination at that time disclosed an enlarged spleen. Two months later roentgen ray therapy was given to the spleen, resulting in a decrease in size of the organ. The following month a few enlarged cervical nodes were noted. Histologic diagnosis on one of these nodes was reported as "lymphoblastoma, probably Hodgkin's disease." Six months later gingival and rectal ulcerations developed. The rectal lesions became abscesses and required surgical incision but were controlled by treatment with penicillin and streptomycin. Anemia was unrelieved by numerous blood transfusions. Despite the extreme neutropenia present, nitrogen mustard therapy was instituted, 20 mg. in four days being given. The response was dramatic, with an immediate subsidence of fever, and the mucosal lesions healed rapidly although no change was noted in the blood count. At this time he began to complain of pain in the feet and toes, and an infiltrative lesion on the skin consisting of erythematous scaling papules involving the toes and tibial crests was noted. This lesion was not affected by the nitrogen mustard therapy; the lesions and associated pain remained, although the general symptoms were markedly improved by the drug. The clinical impression was that of either Hodgkin's cutaneous infiltration or Kaposi's sarcoma. A biopsy had not been performed. During the following six months the patient was given five courses of nitrogen mustard and numerous blood transfusions. During each remission, which lasted from four to five weeks, there were disappearance of fever, improvement in appetite, and a rise in the hemoglobin level. The patient subsequently died, and histologic examination at autopsy disclosed extensive Hodgkin's lesions involving the spleen and lymph nodes and the sternal, rib, and vertebral marrow, with small pulmonary and renal infiltrations. Histologic examination of the skin lesions revealed neoplastic areas in the corium consisting of small, irregular blood vessels in a reticular and fibroblastic framework. The pathologic diagnoses were: (1) Hodgkin's disease of the spleen, lymph nodes, and bone marrow and (2) Kaposi's sarcoma of the skin with lymph node and pulmonary involvement.

Osborne and associates [7] reported the association of Kaposi's sarcoma and Hodgkin's disease in a 67-year-old white woman (Case 7). McCarthy and Pack [8] mentioned one case of the association of Kaposi's sarcoma and Hodgkin's disease. Other cases in which the association was noted have been seen by Erf [9] and Wolf.[10]

*Lymphosarcoma.*—A case of Kaposi's sarcoma which developed into lymphosarcoma was reported by Belloni.[11] McCarthy and Pack [8] reported two cases of Kaposi's sarcoma, one of which was associated with Brill-Symmers disease and the other with lymphosarcoma.

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6. Greenstein, R. H., and Conston, A. S.: Co-Existent Hodgkin's Disease and Kaposi's Sarcoma: Report of a Case with Unusual Clinical Features, Am. J. M. Sc. **218**:384 (Oct.) 1949.

7. Osborne, E. D.; Jordan, J. W.; Hoak, F. C., and Pschierer, F. J.: Nitrogen Mustard Therapy in Cutaneous Blastomatous Diseases, J. A. M. A. **135**:1123 (Dec. 27) 1947.

8. McCarthy, W. D., and Pack, G. T.: Malignant Blood Vessel Tumors: Report of 56 Cases of Angiosarcoma and Kaposi's Sarcoma, Surg., Gynec. & Obst. **91**:465 (Oct.) 1950.

9. Erf, L., cited by Greenstein and Conston.[6]

10. Wolf, J., in discussion on Rosen, I.: Kaposi's Sarcoma Associated with Lymphatic Leukemia, Arch. Dermat. & Syph. **48**:566 (Nov.) 1943.

11. Belloni, M. L.: Maladie de Kaposi à evolution lymphosarcomateuse: Contribution à l'étude des misenchymopathies hyperplastico-néoplasiques, Ann. dermat. et syph. **9**:45 (Jan.-Feb.) 1949.

*Lymphatic Leukemia.*—In 1920, Cole and Crump [12] reported two cases of Kaposi's sarcoma, one of which was complicated by lymphatic leukemia. The patient was a 63-year-old man who had numerous irregularly shaped areas of reddish pigmentation scattered over the entire body, most marked on the lower limbs. These brownish-red and bluish-red areas were usually more pigmented at the periphery and lighter at the center. Both lower limbs were edematous and pitted readily, while along the outer border of the left leg and sole of the left foot the skin was thickly studded with horny, very vascular, bluish nodes which were painful to the touch. When seen three years later this patient presented marked exaggeration of the disease. The papillomatous overgrowths on the lower limbs and on the sole of the left foot had increasd in size, making it impossible for the man to walk. At this time a hemogram disclosed lymphatic leukemia. The authors stated that, to their knowledge, this was the first recorded case of Kaposi's sarcoma in which lymphatic leukemia developed, but they were unable to say whether there was any connection between the two diseases. Although the patient's cutaneous lesions became worse and the leukemia increased in severity, the blood showing over 200,000 white blood cells per cubic millimeter before death, these lesions were not characteristic of leukemia but always distinctive of hemorrhagic sarcoma.

A case of Kaposi's sarcoma and lymphatic leukemia was recorded in 1931 by Hufnagel and Dupont.[13] The patient was a 75-year-old man who had numerous lymphoid nodules of the skin associated with vascular lesions of Kaposi's disease.

Sachs and Gray [14] reported a case of Kaposi's sarcoma and lymphatic leukemia in which there was histologic evidence of the two diseases in the same lesion. Their patient had an eruption of the left sole and instep and the inner aspect of the left heel, of seven months' duration, consisting of irregularly shaped, violaceous plaques 1 to 4 cm. in diameter. There were several smaller lesions on the dorsum of the foot and the toes. Kaposi's sarcoma was present in the middle and upper layers of the cutis and lymphatic leukemia in the deep part of the cutis. The authors believed there are some features which Kaposi's sarcoma and the lymphoblastomas have in common and some ways in which they differ. They stated:

> The former are chiefly from the clinical aspect, while the latter are mainly from the pathologic viewpoint. For example, the two diseases are similar in that both are radiosensitive and both may be present for months or even years. However, the microscopic observations are unlike, for in Kaposi's sarcoma there are angioblasts (endotheloid) and spindle cells, new blood and lymph vessels, development of fibrous tissue and absence of leukocytes. The lymphoblastomas do not have the first three, but they may have the last.

Fischer and Cohen [15] reported the case of a 72-year-old man with Kaposi's sarcoma of the extremities of 25 years' duration. Lymphatic leukemia and diabetes mellitus subsequently occurred.

12. Cole, H. N., and Crump, E. S.: Report of 2 Cases of Idiopathic Hemorrhagic Sarcoma (Kaposi), the First Complicated with Lymphatic Leukemia, Arch. Dermat. & Syph. **1**:283 (March) 1920.

13. Hufnagel, L., and Dupont, A.: Sarcomatose idiopathique de Kaposi et leucémie lymphoïde, Bull. Soc. franç. dermat. et syph. **38**:656 (April) 1931.

14. Sachs, W., and Gray, M.: Kaposi's Sarcoma and Lymphatic Leukemia: Report of a Case, Arch. Dermat. & Syph. **51**:325 (May) 1945.

15. Fischer, J. W., and Cohen, D. M.: Simultaneous Occurrence of Kaposi's Sarcoma, Leukemia and Diabetes Mellitus: Report of a Case, Am. J. Clin. Path. **21**:586 (June) 1951.

In the cases of Cole and Crump,[12] Hufnagel and Dupont,[13] Sachs and Gray,[14] and Fischer and Cohen,[15] the clinical features were those of Kaposi's sarcoma, while the hematologic picture was that of leukemia. Also, all patients died of leukemia and not of idiopathic hemorrhagic sarcoma. Even in the case of Lane and Greenwood,[2] in which the patient had Kaposi's sarcoma and mycosis fungoides, there was evidence of a mild form of lymphatic leukemia. In differentiating lymphatic leukemia from Kaposi's sarcoma, Sachs and Gray [14] suggested an examination of the enlarged lymph nodes. Involvement of lymph nodes, except perhaps regional, is not a feature of Kaposi's sarcoma, and in all cases of such involvement there should be further investigation of the possibility of lymphatic leukemia.

*Myeloid Leukemia.*—A case of Kaposi's sarcoma associated with myeloid leukemia was reported by Tedeschi, Folsom, and Carnicelli.[16] Their patient was a 65-year-old woman who had numerous purpuric areas on the arms and trunk. Kaposi's sarcoma consisted of a mediastinal mass composed mainly of endothelium-lined sinuses and of impervious or canalized endothelial sprouts. These structures were imbedded in a fibrocellular stroma which displayed widespread proliferation of reticulum cells and fibers, fibroblasts, and immature hepatic cells. There were concomitant red blood cell extrasavations, and blood pigment was noted in places.

*Hemolytic Anemia.*—Greppi and Bettoni [17] classified Kaposi's sarcoma with diseases of the reticuloendothelial system. They described an unusual case of Kaposi's sarcoma with extensive visceral involvement and hemolytic splenomegaly. According to the authors the involvement of the reticuloendothelial system in their case had manifested itself in the splenic area, while elsewhere it had given rise to a neoplastic growth with the characteristics of Kaposi's disease.

## COMMENT

On histologic examination of a Kaposi tumor there is evidence of hemorrhage; newly formed blood vessels, including proliferation of endothelium and adventitial connective tissue; spindle cells, and cellular infiltration, including early lymphoid elements and reticulum. What tissue other than that of reticuloendothelial system presents such a diversity of structures? The reticuloendothelial origin of Kaposi's sarcoma was advanced as long ago as 1911 by Dalla Favera.[18] Others who advanced this etiological concept of Kaposi's sarcoma are Dillard and Weidman,[19] Puhr,[20] Dorffel,[21] Dupont,[22] Goldsmith,[23] Becker and Thatcher,[24] Choisser and

16. Tedeschi, C. G.; Folsom, H. F., and Carnicelli, T. J.: Visceral Kaposi's Disease, Arch. Path. **43**:335 (April) 1947.

17. Greppi, E., and Bettoni, I.: Splenomegalia emolitica ed angio-endothelioma cutaneo tipo Kaposi con associazione di agranulocitosi e sepsi orale: Sindrome complessa di reticoloendoteliosi iperplastico-neoplastica, Arch. Ist. biochem. ital. **4**:403 (Nov.) 1932.

18. Dalla Favera, G. B.: Über das sogenannte Sarcoma idiopathicum multiplex hæmorrhagicum (Kaposi), Arch. Dermat. u. Syph. **109**:387, 1911.

19. Dillard, G. J., and Weidman, F. D.: Multiple Hemorrhagic Sarcoma of Kaposi: Histologic Studies of 2 Cases at Necropsy, Arch. Dermat. & Syph. **11**:203 (Feb.) 1925.

20. Puhr, L.: Über das idiopathische multiple Pigmentsarkom der Haut (Kaposi), Arch. Dermat. u. Syph. **164**:167, 1931.

21. Dorffel, J.: Histogenesis of Multiple Idiopathic Hemorrhagic Sarcoma, Arch. Dermat. & Syph. **26**:608 (Oct.) 1932.

*(Footnotes continued on next page)*

Ramsey,[25] Lane and Greenwood,[2] Greenstein and Conston,[6] Greppi and Bettoni,[17] Goldschlag,[4b] and Tedeschi and associates.[16] It is the last-mentioned group of writers who advanced the concept that Kaposi's disease is "systemic in nature and likely to involve independently and in an unpredictable manner, simultaneously or successively, the skin and the internal organs and that it is characterized from the histologic standpoint by a great variety of patterns inherent to the multiple developmental potentialities of the basic unit of growth, the reticulum cell." Dorffel,[21] too, believed that the cell type involved is basically the pluripotent cell of the reticuloendothelial system which, owing to its various developmental potentialities, is able to give rise to complex and unpredictable structures. He concluded that sarcoma of Kaposi is a disease of the reticuloendothelial system, including a disturbance in its monocytogenetic function, which at times may terminate in true malignancy. He supported this belief with the following points of evidence: (1) the vascular system throughout the body is the site of definite clinical changes, such as ectasia, varicosities, and purpuric lesions; (2) nodules may be found distributed along the vessels and adherent to the vessels; (3) microscopically, newly formed capillaries and a polymorphous cellular infiltrate are found, the cells of which arise from the reticuloendothelial system (lymphocytoid cells); (4) the monocyte system is affected, as evidenced by an increased number of monocytes in the tissues and monocytosis in the differential blood smear, and (5) the presence of gitterfasern does not permit too definite conclusions on this point. Goldschlag [4b] suggested that this group of diseases would perhaps be better classed under the heading of "reticuloendothelioses" rather than "lymphoblastomas."

Another unusual fact is the comparative rarity of Kaposi's disease in the American Negro. In 1931 Pardo-Castelló [26] reported a case in a full-blooded Negro, and in 1932 Andrews [27] presented a case in an American mulatto. Ellis [28] presented a case in a full-blooded Negro. Others who have reported cases in Negroes are Loewenthal,[29] Garner,[30] Symmers,[31] Aegerter and Peale,[32] Persky and Lisa,[33] Hazen,[34] Brunsting,[35] and Smith and Samitz.[36]

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22. Dupont, A.: Note sur la maladie de Kaposi (sarcomatose multiple idiopathique pigmentaire), Bull. Assoc. franç. étude cancer **23**:487 (June) 1934.

23. Goldsmith, W. N.: The Reticuloses, Brit. J. Dermat. **56**:104 (May-June) 1944.

24. Becker, S. W., and Thatcher, H. W. L.: Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi: Historical Review, Nomenclature, and Theories Relative to Nature of the Disease, with Experimental Studies of 2 Cases, J. Invest. Dermat. **1**:379 (Oct.) 1938.

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*(Footnotes continued on next page)*

According to Findlay,[37] Kaposi's sarcoma is not particularly rare in the Belgian Congo, since there is an occurrence of at least one case in 50,000 among the adult population. Kaminer and Murray[38] stated that 41 cases have been reported in Bantu men. The relatively high incidence of Kaposi's disease in Bantu men is in striking contrast to the few cases that have been reported in American Negroes. Kaminer and Murray considered the possibility of a genetic factor, particularly since the sickle-cell trait is rare in the Bantu.

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# PARALLEL RELATION OF HYPERGLYCEMIA AND HYPERLIPEMIA (ESTERIFIED FATTY ACIDS) IN DIABETES

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THE INDEX used for many years to guide the management of diabetes mellitus was the efficacy with which the excretion of glucose in the urine could be controlled. When methods for measuring the glucose content of the blood were devised, the maintenance of the sugar of the blood at normal levels became the objective. The metabolism of both carbohydrates and fats in diabetes mellitus is abnormal, and the blood of a patient with severe diabetes is hyperlipemic. The pattern of the hyperlipemias in diabetes mellitus has not been investigated because systems of blood analysis do not include methods for the fractional estimation of the lipids in small amounts of blood comparable in precision to those with which the glucose content of the blood is measured. Methods for estimating the cholesterol content of the blood have been available for many years, and clinicians have taken the cholesterol level of the blood as an index for the entire lipid fraction. However, fractional analyses of the hyperlipemic blood of animals made diabetic by removal of pancreas tissues and similar examinations of the blood lipids of human diabetics have disclosed that the triglyceride fraction in diabetic lipemias is increased most, while the cholesterol and phospholipid fractions are increased but slightly or not at all.[1]

Bauer and Hirsch [2] reported the levels of the esterified fatty acids in 102 presumably healthy human adults, determined by a colorimetric method which they had devised.[3] Their analyses were made on blood drawn before breakfast from men and women who had taken no food since the preceding evening. The maximum level of the esterified fatty acids in this group was 12.6, the minimum was 7.0, and the mean was 9.2 mEq. per liter of serum. This range, of course, applies only to a postprandial interval of this number of hours.

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From the Henry Baird Favill Laboratory of St. Luke's Hospital and the Department of Pathology of the University of Chicago.

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Hirsch and Carbonaro then studied the postprandial lipemias of normal human adults and of diabetics.[1] They gave a fat meal consisting of 36% cream (largest portion), unsalted butter, bacon, water-packed fruit, gluten bread, and coffee, but no sugar, in the amounts of 2 or 3 gm. fat per kilogram of body weight. This test meal was given in the morning, about 14 hours after the meal of the evening before. At 8 a. m. the first sample of blood was drawn, and between 8 and 9 a. m. the test meal was eaten. Seven samples of blood were drawn thereafter at intervals of one hour while the subject was at rest. Hirsch and Carbonaro observed in health an appreciable increase of the serum esterified fatty acids following such a meal of fat. The increment of increase was not the same, nor was it reached within the same time, in the various persons tested; also, the increase was greater in the same person with the 3 gm. fat per kilogram than with the 2 gm. per kilogram ratio. The peak level of the serum fatty acids was reached usually by the third to fourth hour after the meal was taken. After the maximum level was reached the serum fatty acids declined toward the initial level. Among the 28 tests completed for 21 normal human volunteers, the maximum level of the serum fatty acids in 10 tests was reached in three hours, in another 10 tests in four hours, in 4 tests by the second hour, in 3 tests by the fifth hour, and in 1 test within one hour. The initial fatty acid content of the serum in the 28 tests on the 21 human volunteers ranged between 7.1 and 10.8 and averaged 8.8 mEq. per liter of serum. These initial values represent the fatty acid content of the blood under the conditions of the experiments and not the lowest level to which the fatty acids would fall after a longer interval without food. The postprandial (fat meal) increase in percentage of the esterified fatty acids of the blood above the initial so-called fasting level in the 28 tests on the 21 normal adults ranged in 5 tests between 104 and 146, in 7 tests between 71 and 89, and in 16 tests between 24 and 64. The total cholesterol content of the serum measured simultaneously with determination of the fatty acid content varied but slightly from the initial value in each test. Accordingly, the cholesterol content of the serum is not an index of the total lipid content of the serum in the postprandial lipemias. The amount of the postprandial lipemia also varies individually, and among healthy adults are those with marked, intermediate, and small elevations of the serum esterified fatty acids.

Hirsch and Carbonaro [1] studied similarly the postprandial lipemia in 21 diabetics. Among these were 13 with mild diabetes mellitus. The initial level of the serum esterified fatty acids, with or without insulin, was in the high range for healthy adults, and the peak level following the test meal ranged in the highest levels observed in the normal group. This maximum level was reached later than in the fat-tolerance tests of the normal adults. The duration of the postprandial lipemia, therefore, was longer. The cholesterol content of the serum in the persons with mild diabetes did not change significantly from the initial level. The eight patients with severe diabetes mellitus, all using insulin, had a similar but more marked increase of the esterified fatty acids of the serum following the test meal of fat. The initial serum fatty acid content was above the highest initial values observed in the normal group and even exceeded the maximum postprandial level of several. The maximum level was reached late and was several or even many times that of the healthy group. Thus, in severe diabetes the postprandial lipemia is prolonged and the percentage increase over the initial high value is large. The cholesterol analyses in each of these fat-tolerance tests gave no indication of the postprandial lipemia which the quanti-

tative analyses of the esterified fatty acids of the serum disclosed. The level of glucose in the blood during the seven hours required for the test did not change appreciably.

The need for careful regulation of the diet and insulin control of the diabetic is now in dispute among clinicians. The one group [4] holds that the blood sugar of the diabetic should be maintained as near to the normal level as is possible by diet regulation and insulin control. The other group argues that the diabetic's hyperglycemia and glycosuria do not make him more susceptible to infection, coma, or vascular disease, and hence he should have a free diet and protamine insulin as prescribed. Tolstoi [5] advocated this form of management and stated that the patient need not be concerned with blood sugar determinations and the "gadgets" for urine analysis. Tolstoi experienced difficulties with patients when he tried to adjust the glycosuria too finely or to maintain the urine free from sugar. There is no evidence, he stated, that hyperglycemia and glycosuria are etiologic factors in vascular degenerative lesions. This comment seems to be facetious, because pathologists never have regarded glucose circulating in the blood as a cause of atherosclerosis. All investigators of atherosclerosis, however, are much concerned with the role of the circulating lipids in the causation of this vascular disorder both in the diabetic and in the average human adult.

The incidence of the two most commonly observed vascular complications, retinopathy and calcification of peripheral arteries, has been used in statistical analyses as the index for determining good or poor management of diabetics. Obviously this is a crude standard and can be used only in groups of diabetics who have been managed for many years, because 10 to 15 years of diabetes mellitus are required for the development of these degenerative vascular lesions. Both the proponents and the opponents of the controlled management of diabetes thus use an index that can be controversial. Regardless of whether the lipid deposits of blood vessels are primary and in that sense the direct cause of atherosclerosis or are secondary to an injury of the tissues in the vessel wall, current views hold that the circulating lipids of the blood, their characteristics and quantity, have marked significance in the evolution of this vascular disorder.

Current views applied to the marked incidence of atherosclerosis among diabetics suggest a direct causal relation of the lipemia in diabetes mellitus to the evolution of the arterial disease in these patients. This conclusion, of course, is implied if not expressed in the clinical evaluations of diabetic management based on conditions such as retinopathy and evidence of calcification of peripheral arteries. Since lipemias, specifically those of diabetes mellitus, have this significance, a study of them in diabetics under conditions of blood sugar control and when the patients are hyperglycemic may afford information that will indicate which is the better procedure for the management of diabetics.

## METHODS

The method described by Bauer and Hirsch[3] was followed in determining the esterified fatty acids of the blood; the sugar and cholesterol estimations were made according to the

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method of Folin and Wu adapted for spectrophotometric analysis. The fatty acid and glucose levels of the blood were determined under varying conditions in the diabetic patients as follows:

1. *During the Hyperglycemia Following the Withholding of Insulin.*—The so-called fasting level of the lipids was determined during a control interval when the sugar of the blood was maintained within the normal range. Insulin was then withheld for intervals varying from a few days to several weeks, until a significant hyperglycemia had developed. The hyperglycemia was allowed to continue at least 4 days and in some patients 10 days, and then insulin therapy was reinstituted and carried on until the blood sugar level had returned to the normal range. Blood lipid and sugar determinations were made daily during this time. The patients were maintained on an average liberal diet.

2. *During Fat Tolerance After Meals of Fat When the Patient Was Hypoglycemic and Again When He Was Normoglycemic.*—Hyperglycemia was allowed to develop in diabetic patients by withholding insulin. After a week or more of hyperglycemia a fat-tolerance test using 3 gm. fat per kilogram of body weight was made. Then insulin was given, and after the sugar level of the blood had been normal for some time a second fat-tolerance test was made. In one patient the sequence was reversed, and the first fat-tolerance test was made when the blood sugar values were in the normal range and the second test after two weeks of hyperglycemia.

3. *During a Period of Observation When the Sugar of the Blood Fluctuated Widely.*—A diabetic who had wide fluctuations in blood sugar and required varying amounts of insulin was studied in the hospital for an extended time, and daily so-called fasting blood lipid and sugar determinations were made. The diet of this patient varied widely in caloric intake, and there were transient periods of acetonuria, none lasting more than 12 hours.

4. *During Modifications of the Blood Sugar by Insulin or Diet Control or Both.*—Two patients with severe diabetes were studied. In each, hyperglycemia was induced by withholding insulin. After a week of hyperglycemia, a small amount (10 units) of protamine zinc insulin was administered daily and the caloric intake was increased to 2,500 calories, an amount sufficient to maintain hyperglycemia. After 10 days the diet was reduced to approximately 650 calories without change in the insulin. In one case, after the blood sugar had been at a high-normal level for five days the insulin was increased to 55 units daily for 10 days more. In the second case, use of insulin was suspended after the blood sugar had reached a normal level with the 647-calory diet and the blood sugar and lipid levels were determined for 11 days more with only diet control.

## EXPERIMENTS

### Group 1

Case 1.—The mild diabetes of a Negro woman was controlled with 24 units of protamine zinc insulin and a daily diet of 200 mg. carbohydrate, 100 gm. protein and 100 gm. fat. The control fasting blood sugar was 114 and 117 mg. per 100 ml. and the esterified fatty acids 18.0 and 16.0 mEq. per liter. The fasting blood sugar without insulin control gradually rose in five weeks to 254 mg. per 100 ml. and the lipid fraction to 21.2 mEq. per liter. Insulin was given, and within 19 days the fasting blood sugar was 150 mg. per 100 ml. and the fatty acids 14.5 mEq. per liter.

Case 2.—The diabetes of a white woman under hospital care was controlled with 55 units of protamine zinc insulin and a diet of 152 gm. of carbohydrate, 89 gm. of protein, and 70 gm. of fat. Control fasting blood sugar levels were 134 and 55 gm. per 100 ml., and the lipid fraction was 9.7 and 7.8 mEq. per liter. After five days without insulin the fasting blood sugar was 470 mg. per 100 ml. and the lipid fraction had risen to 18.0 mEq. per liter. On the sixth day insulin was given, and within five days the fasting blood sugar was 154 mg. per 100 ml. and the fatty acids 12.7 mEq. per liter (Chart 1).

Case 3.—The diabetes of a white woman on a diet of 174 gm. of carbohydrate, 82 gm. of protein, and 70 gm. of fat was controlled with 52 units of protamine zinc insulin. The fasting blood sugar was 128 gm. per 100 ml., and the serum fatty acids were 12.1 mEq. per liter. After 10 days without insulin the fasting blood sugar had risen to 344 mg. per 100 ml. and the lipid fraction to 14.5 mEq. per liter. Through an error 20 units of regular insulin was given on the seventh day, and on the following morning the fasting blood sugar had fallen from the 300 mg. of the day before to 180 mg. per 100 ml. and the lipid fraction from 14.0 to 12.5 mEq. per liter (Chart 2).

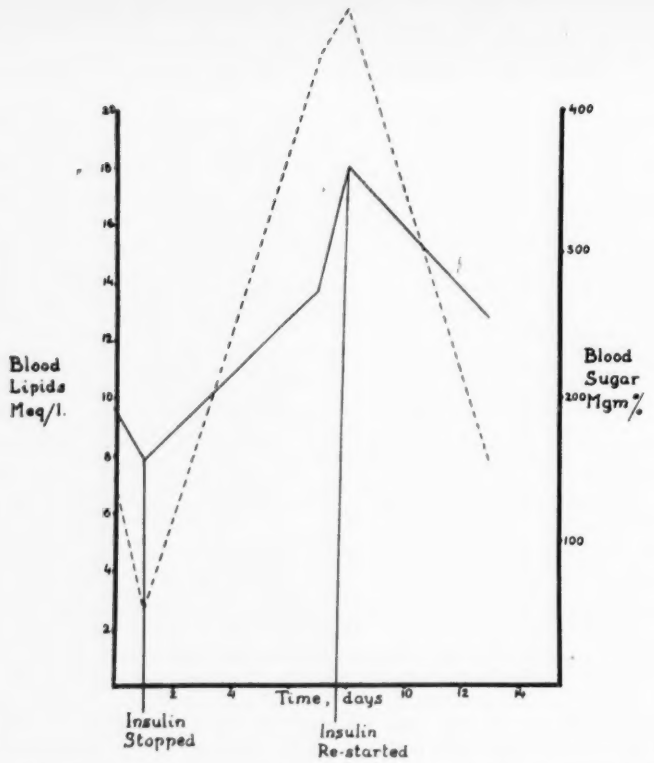


Chart 1 (Case 2).—Graphs illustrating the parallel rise and fall of esterified fatty acids (unbroken line) and glucose (broken line) of the blood during hyperglycemia and normoglycemia in diabetes mellitus.

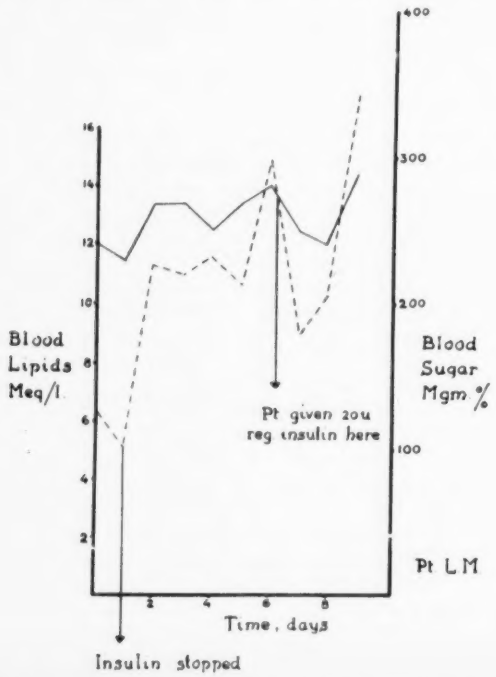


Chart 2 (Case 3).—Graphs illustrating parallel relations between hyperlipemia (unbroken line) and hyperglycemia (broken line) and the insulin effect on both in diabetes mellitus.

CASE 4.—A diabetic Negro woman on a control diet and 69 units of protamine zinc insulin had a fasting blood sugar level of 91.5 mg. per 100 ml. and 11.2 mEq. per liter of fatty acids. After four days without insulin the glucose of the blood had risen to 360 mg. per 100 ml. and the lipid fraction to 17.6 mEq. per liter. On the fifth day insulin was given again, and after four days the fasting blood sugar had dropped to 93 mg. per 100 ml. and the fatty acids to 13.1 mEq. per liter. For some reason not apparent, the fasting blood sugar on the fifth day was 235 mg. per 100 ml. and the lipid fraction was 12.1 mEq. per liter. This is the only observation of a rise in blood sugar without a change in lipid fraction. Other analyses might have disclosed a lag or reasonable explanation (Chart 3).

GROUP 2

CASE 5.—A diabetic Negro woman was under management in the hospital with 54 units of NPH insulin daily and a diet of 1,200 calories containing carbohydrate 100 gm., protein 60 gm., and fat 60 gm. Under these conditions a fat-tolerance test was done. The blood sugar at the beginning and at the end of the test was 126 mg. and 87 mg. per 100 ml. The fatty acids of the blood rose from 17.8 mEq. per liter and after seven hours had reached 50.7 mEq. per liter. The plotted results of the lipid fraction formed a curve characteristic of diabetes. After a week without insulin, when the patient was in a stage of hyperglycemia, the second fat-tolerance test was done. The blood sugar at the beginning and at the end of the test was 285 and 300 mg. per 100 ml. The fasting serum fatty acids were 22.8 and reached 60 mEq. per liter, all values being much higher than when the patient was normoglycemic.

CASE 6.—A diabetic Negro woman after five days in the hospital without insulin had a fasting blood sugar level of 354 mg. per 100 ml. Then a fat-tolerance test was made. The blood sugar level at the beginning was 285 mg. per 100 ml. and at the end 354; the fatty acids began at 30 mEq. per liter and rose to 70.2. Within two weeks of insulin therapy and diet restriction the patient was normoglycemic. After five days of a normal blood sugar level a second fat-tolerance test was done. The blood sugar at the start and at the finish of the test was 131 mg. per 100 ml. The fatty acid fraction initially was 15.0 mEq. per liter and rose to 34.2 at the end (Chart 4).

CASE 7.—A diabetic Negro woman had been out of diabetic management for several weeks before entering the hospital, and initially no insulin was given. After five days of hyperglycemia the fat-tolerance test was done. The glucose of the blood at the beginning was 227 mg. per 100 ml. and at the end 200; the fatty acids initially were 18.8 mEq. per liter and rose to 62.0. With dietary restriction and insulin administration the blood sugar became normal. After 21 days of normoglycemia, the last 11 days without insulin and with a 650-calorie diet, a second fat-tolerance test was done. The blood sugar at the beginning and at the end of the test was 131 and 117 mg. per 100 ml. The lipid fraction, lower than during the first test, began at 11.8 mEq. per liter and rose to 32.1 at the end (Chart 5).

GROUP 3

CASE 8.—A cancerous white woman aged 64 years had diabetes mellitus that was difficult to control. Her daily food intake varied and the dosage of insulin was changed frequently and markedly because of the fluctuations in her blood sugar. The fasting blood sugar and serum fatty acids were determined daily for six weeks. Every rise and fall in the fasting blood sugar had a parallel rise and fall of the lipid fraction (Chart 6). The presence of acetonuria had no influence.

GROUP 4

CASE 9.—A diabetic Negro woman became hyperglycemic from witholding of insulin. After five days of hyperglycemia, 10 units of protamine zinc insulin was given daily and the hyperglycemia was maintained by increasing the diet to 2,500 calories. The fasting blood sugar level remained high (376 mg. per 100 ml.) and the fatty acid level also (46.9 to 25.4 mEq per liter). On the sixth day of this regimen the diet was reduced to 600 calories without changing the insulin. The sugar and the lipid fraction decreased slightly but remained high during the next six days. The insulin was then increased to 55 units daily, and in 10 days the fasting blood sugar became 150 mg. per 100 ml. and the fatty acids 14.2 mEq. per liter (Chart 7).

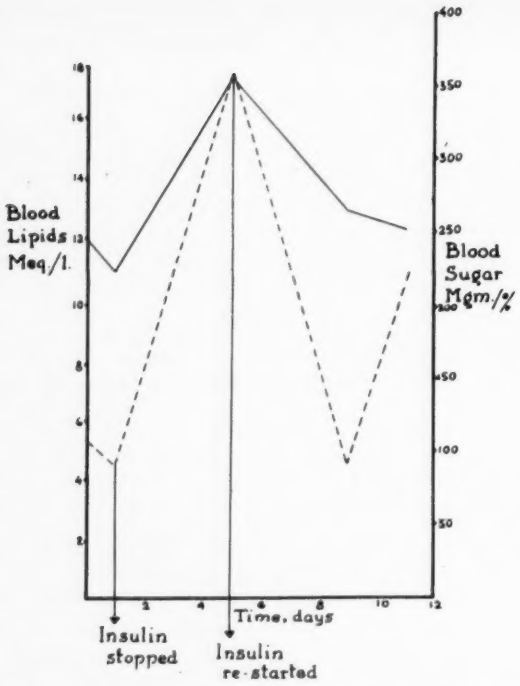


Chart 3 (Case 4).—Graphs illustrating again the parallel rise of the sugar (broken line) and esterified fatty acids (unbroken line) in the blood of a diabetic without diet or insulin control.

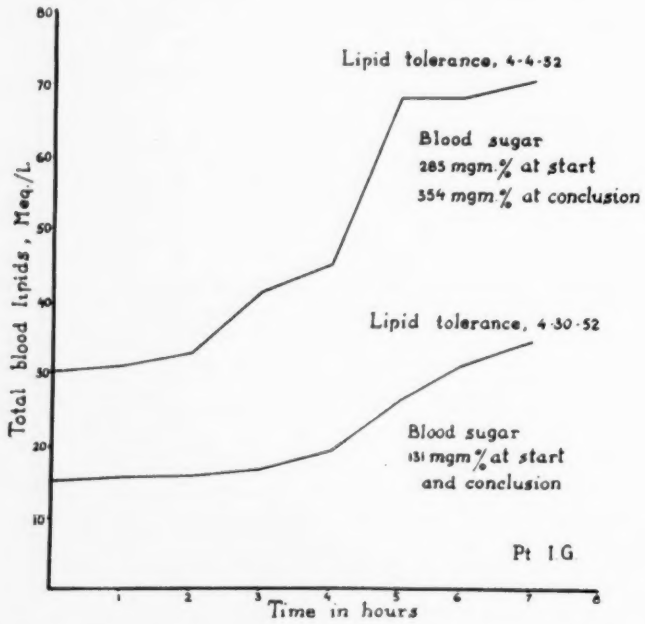


Chart 4 (Case 6).—Graphs illustrating increase of fatty acids of the blood after a fat-tolerance test meal of 3 mg. of fat per kilogram of body weight in a diabetic during normoglycemia and hyperglycemia. The graphs illustrate a high initial fasting level and a prolonged marked rise of fatty acids—a typical diabetic curve with this test. Note that comparable values for fatty acids were much greater during hyperglycemia than during normoglycemia.

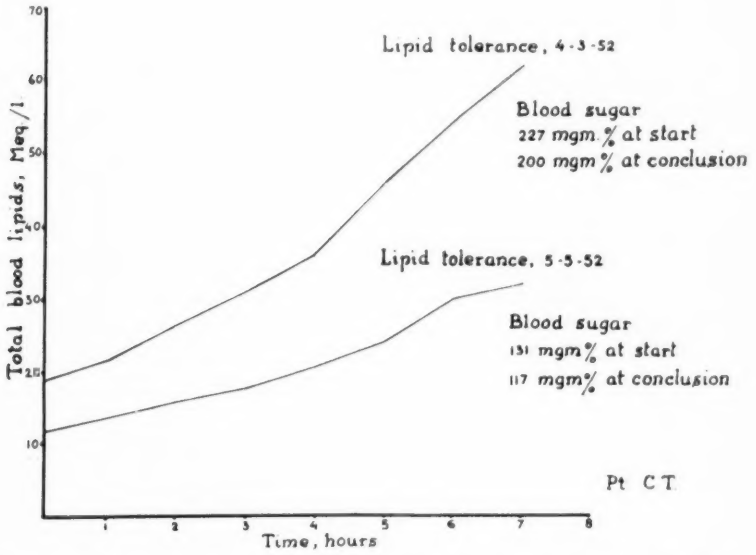


Chart 5 (Case 7).—Graphs contrasting the postprandial increase of fatty acids of the blood in a fat-tolerance test on a diabetic during normoglycemia and during hyperglycemia.

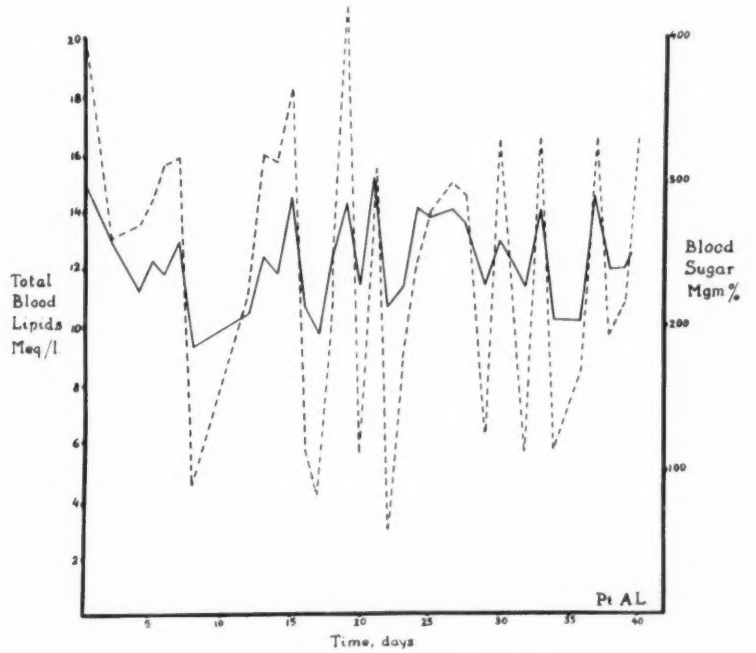


Chart 6 (Case 8).—Graphs illustrating the parallel fluctuations of fatty acids (unbroken line) and glucose (broken line) in a diabetic difficult to control by diet and insulin. Note that with each rise and fall in blood sugar a coincidental rise and fall in blood lipids occurred.

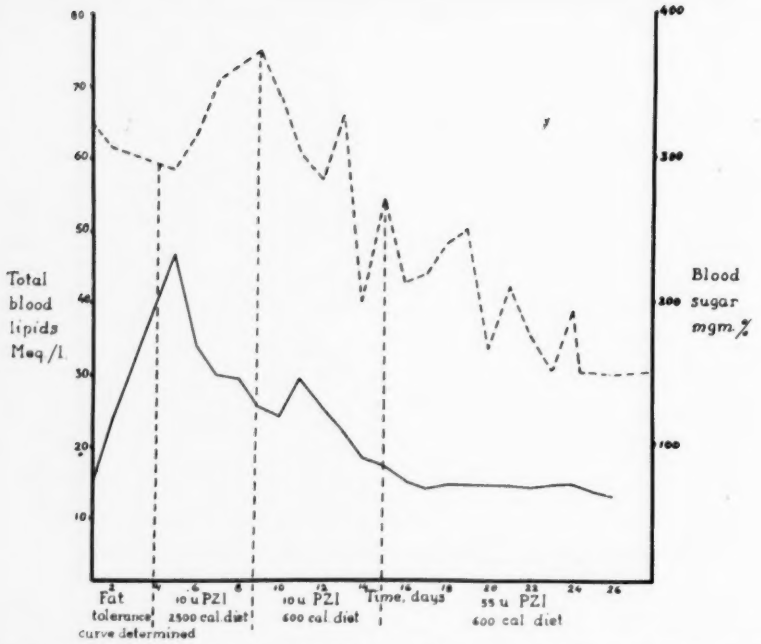
Total blood lipids Meq/l.
Blood sugar mgm.%
Fat tolerance curve determined
10 u PZI 2500 cal. diet
10 u PZI 600 cal. diet
Time, days
55 u PZI 600 cal. diet

Chart 7 (Case 9).—Graphs illustrating the parallel relations of fatty acid (unbroken line) and glucose (broken line) content of the blood of a diabetic under varying conditions of diet and insulin management.

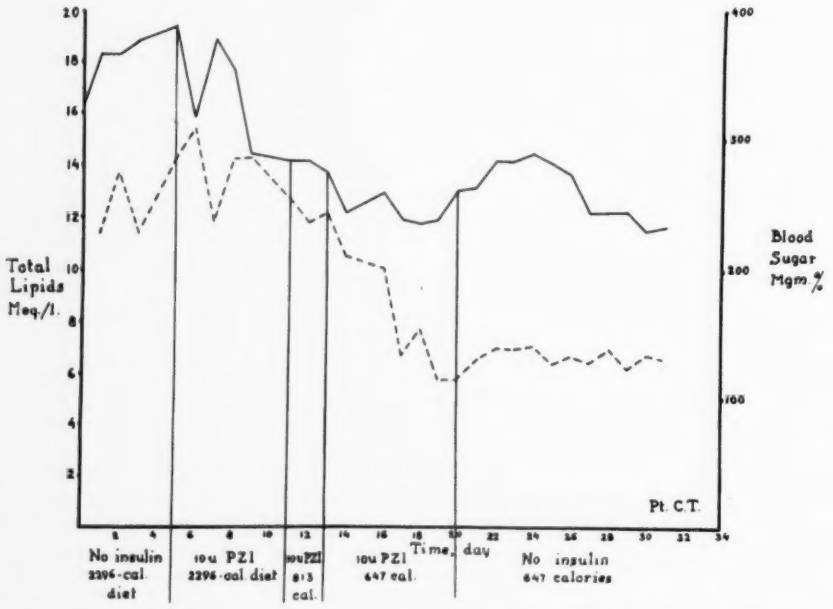


Chart 8 (Case 10).—Graphs illustrating parallel relations between fatty acid (unbroken line) and glucose (broken line) content of the blood in another diabetic with varying degrees of diet and insulin control.

CASE 10.—Hyperglycemia was induced in a diabetic Negro woman by withholding insulin. After five days of significant hyperglycemia she received 10 units daily of protamine zinc insulin. The fasting blood sugar level remained high (308 mg. per 100 ml.) and the fatty acid level also (19.3 mEq. per liter). After 10 days the diet was reduced to 813 calories daily and two days later to 647 calories, the insulin dosage remaining the same. Within seven days of this regimen the fasting blood sugar fell to 114 mg. per 100 ml. and the lipid fraction to 12.2 mEq. per liter. Then, for another 11 days, the 647-calorie diet was continued without insulin. The fasting blood sugar remained within the normal range, 124 to 142 mg. per 100 ml., and the lipid fraction was 12.2 to 14.2 mEq. per liter (Chart 8).

### COMMENTS

The hyperglycemia induced in four diabetics of Group 1 by withholding insulin was associated with a rise of the esterified fatty acids of the blood which paralleled closely in time and intensity the increase of the blood sugar. When the blood sugar was reduced to normal with insulin the lipid fraction also returned to normal.

The fat-tolerance tests on four diabetic patients of Group 2 also disclose a close relation between hyperglycemia and hyperlipemia. These tests were made on diabetics when the sugar of the blood was at normal levels and when there had been hyperglycemia for days or weeks. The lipid values obtained at both levels of the blood sugar when plotted form a typical diabetic curve, that is, an initially high fasting level of the fatty acids followed by a marked and prolonged rise. In the fat-tolerance tests of four patients, each lipid value in the test series when the patient was hyperglycemic was much higher than the corresponding value in the test series when the patient was normoglycemic.

During the six weeks of study every rise and fall of the fasting blood sugar of the patient with diabetes (Group 3) difficult to control was associated with a coincidental rise and fall of the esterified fatty acids.

The fluctuations of the blood sugar in the diabetics of Group 4 induced by variations in diet and insulin dosage were associated with parallel fluctuations of the lipid fraction of the blood.

Cholesterol determinations on the blood made coincidentally with the sugar and fatty-acid analyses in all these groups of patients disclosed no significant or correlated fluctuations.

### COMMENT

These results show clearly that hyperglycemia in diabetic patients is associated with a marked elevation of the esterified fatty acids of the blood. When a hyperglycemic diabetic becomes normoglycemic through diet or insulin control or both, the lipid fraction returns to the normal range. When a standard fat-tolerance test is made on a diabetic during hyperglycemia, each individual fatty acid value is much higher—and is apparently in proportion to the degree of hyperglycemia—than the corresponding value obtained when the fat-tolerance examination is made during normoglycemia.

These observations, establishing a direct relation between hyperglycemia and hyperlipemia in diabetes mellitus, provide information that is significant in a decision as to whether the blood sugar of a diabetic should or should not be maintained within the normal range. The evidence so far offered in support of the two opposite views has been statistical, based on the presence of degenerative vascular disease in the retina and peripheral blood vessels in diabetics who have been under observation for

at least 15 years. The interpretation of statistical data on diabetic patients who are examined for degenerative vascular disease after 15 or more years, during which time significant variations in diet and insulin requirements may have passed unrecognized, certainly can be controversial. All investigators of atherosclerosis ascribe great significance to the blood lipids in the evolution of the disease. The high incidence of atherosclerosis in diabetics has been known for many years and was observed especially during the years when a high-fat diet was recommended. Hyperlipemia in the diabetic, accordingly, cannot be dismissed as insignificant in the evolution of this disease. Weinhouse and Hirsch [6] in a chemical study of the changes in the aorta of human adults with atherosclerosis reported the results shown in Table 1.

TABLE 1.—*Average Values of Constituents of Intimal Lesions*

| | | | Composition of Lipid Extract Corrected for Ash Content | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Phosphatide ‡ | | | | |
| Type of Lesion | Moisture * | Lipid Extract † | Cholesterol ‡ Free | Cholesterol ‡ Ester | Ether, Soluble | Ether, Insoluble | Total | Galactoside ‡ | Fatty Acids, Neutral Fat, Etc.‡ |
| Normal intima | 71.6 | 14.4 | 14.2 | 38.6 | 13.7 | 6.4 | 20.1 | 8.0 | 19.1 |
| Early fatty plaques | 67.5 | 25.9 | 16.2 | 38.5 | 10.8 | 8.2 | 19.0 | 5.8 | 20.5 |
| Fibrous plaques | 66.5 | 27.2 | 18.1 | 47.5 | 5.9 | 9.0 | 14.9 | 4.5 | 15.0 |

* The content is given as percentage of wet tissue.
† The content is given as percentage of dry tissue.
‡ The content is given as percentage of total lipid.

TABLE 2.—*Comparison of Lipid Composition of Blood Plasma and Arterial Tissue*

| | Blood Plasma | Intima | Early Plaques |
|---|---|---|---|
| Free cholesterol | 14.1 | 14.2 | 16.2 |
| Cholesterol esters | 38.3 | 38.6 | 38.5 |
| Phospholipids | 22.8 | 20.1 | 19.0 |
| Neutral fat, etc. | 23.3 | 27.1 | 26.3 |

* The values are given as percentages of total lipid.

The close agreement in the composition of the lipids extracted from the normal intima, the intima tissues with the fatty deposits, and the intima with fibrous and fatty plaques of atherosclerosis suggests that the lipids infiltrate from the blood stream. A comparison of their analyses with those of the lipids of the blood published by Page, Kirk, Lewis, Thompson, and Van Slyke [7] reveals a striking agreement.

This comparison (Table 2) supports the view that the intima is freely permeable to the lipids of the plasma and has no selective affinity for them. The close agreement between the composition of the extracts of the normal intima and that of the fatty deposits in the intima suggests further that these deposits arise through the non-

6. Weinhouse, S., and Hirsch, E. F.: Chemistry of Atherosclerosis: I. Lipid and Calcium Content of the Intima and of the Media of the Aorta With and Without Atherosclerosis, Arch. Path. **29**:31 (Jan.) 1940.

7. Page, I. H.; Kirk, E.; Lewis, W. H.; Thompson, W. R., and Van Slyke, D. D.: Plasma Lipids of Normal Men at Different Ages, J. Biol. Chem. **111**:613 (Nov.) 1935.

specific deposition of the plasma lipids. Hirsch and Weinhouse [8] in their review of the role of lipids in atherosclerosis discussed many of the basic elements of the problem. They concluded that lipids circulating in the blood and conditions in the lining tissues of the blood vessels favoring the deposition of the lipids in the plasma are important factors in the evolution of the disease. More recently Gofman and his associates [9] have sought to establish a causal relationship between the presence in the blood of lipid molecules of $S_f$ 10 to 20 size and atherosclerosis.

SUMMARY

Hyperglycemia in the human diabetic is associated with a hyperlipemia the intensity of which seems to approximate the severity of the hyperglycemia.

In the hyperlipemias of diabetes mellitus, the triglyceride fraction of the blood lipids is increased the most and the cholesterol and the phosphatides slightly or not at all.

When a hyperglycemic diabetic becomes normoglycemic through diet or insulin control or both, the esterified fatty acids of the blood return to the high-normal range.

The values for the esterified fatty acids of the blood obtained during a fat-tolerance test are much higher when the diabetic is hyperglycemic than when he is normoglycemic.

The significance of hyperlipemia in the evolution of atherosclerosis in diabetics is discussed briefly. The demonstration that hyperglycemia in a diabetic is associated with a parallel and apparently proportional hyperlipemia emphasizes that maintenance of the blood sugar of diabetic patients at normal levels controls the lipid content of the blood. According to current views on the role of the lipids in the evolution of atherosclerosis, the maintenance of the blood lipids in diabetics at or near the high-normal range is significant in delaying the evolution of degenerative vascular disorders.

8. Hirsch, E. F., and Weinhouse, S.: The Role of the Lipids in Atherosclerosis, Physiol. Rev. **23**:185 (July) 1943.

9. Gofman, J. W.; Jones, H. B.; Lindgren, F. T.; Elliott, H. A., and Strisower, B.: Blood Lipids and Human Atherosclerosis, Circulation **2**:161 (Aug.) 1950.

# Progress in Internal Medicine

## HYPERTENSION

**Review of Significant Publications, July 1, 1950, to Jan. 1, 1952**

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THE PURPOSE of this paper is to present a brief, integrated synopsis of articles on arterial hypertension in the medical literature published from July 1, 1950, to Jan. 1, 1952. It is not the purpose to mention every item in that literature. While this admittedly may have a personal point of view, not to say bias, we hope that it will stimulate the reader rather than bore him with a mere recital of the published reports. The material in this paper will be considered under the following general headings: Etiology and Pathogenesis, Pathologic Physiology, Pathologic Anatomy, Course and Prognosis, and Treatment. Two interesting symposia on hypertension have been published in 1951 which give background material as well as recent work.[1]

### ETIOLOGY AND PATHOGENESIS

The etiology of essential hypertension remains unknown. Nothing basically new has been added to previous ideas of pathogenic mechanisms in elevated blood pressure. These mechanisms remain as before: (1) renal, (2) humoral, (3) neurogenic, and (4) hereditary.

*Renal Factors.*—This subject still receives more attention than any other in the field of arterial hypertension, and well it may, for if we know anything about hypertension, we know that the kidney is involved, if not primarily then usually secondarily, in the process. The primary role of the kidney in clinical hypertension is clearest in the relatively rare cases in which removal of a unilaterally diseased kidney restores blood pressure to normal. These cases [2] continue to give support to

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1. Hypertension: A Symposium, edited by E. T. Bell, Minneapolis, University of Minnesota Press, 1951. A Symposium on Essential Hypertension: An Epidemiologic Approach, Boston, The Commonwealth of Massachusetts, 1951.

2. (*a*) Mathisen, H. S.: Arterial Hypertension in Unilateral Renal Disease with Inhibition of Growth, Treated with Nephrectomy, Acta med. scandinav. **139**:421, 1951. (*b*) Burkland, C. E.; Goodwin, W. E., and Leadbetter, W. F.: Cure of Hypertension by Nephrectomy: A 10-year Follow-Up of a Case, Surgery **28**:67 (July) 1950. (*c*) Pulaski, J. E.: Perirenal Lymphangioma Causing Hypertension, Ann. Int. Med. **33**:234 (July) 1950. (*d*) Adams, L. J.; Notkin, M., and Pritchard, J. E.: Hypertension in 2 Cases of Renal Artery Occlusion, Canad. M. A. J. **64**:224 (March) 1951. (*e*) Gerbaux, A.: L'hypertension artérielle d'origine rénale curable par néphrectomie chez l'homme, Semaine hôp. Paris **26**:715 (Feb. 28) 1950.

the Goldblatt experiment as a cause of human hypertension, but mainly as a clinical rarity rather than as a common occurrence. Of 275 such cases collected from the literature nephrectomy relieved the hypertension completely in 25%, partially in 14%, and not at all in 61%.[2e] Hypertension secondary to bilateral diffuse glomerulonephritis and pyelonephritis is a much more frequent if a more benign condition.[3]

Experimental renal hypertension continues to be of major interest through numerous efforts to produce it and to explain it. Thus, arterial hypertension develops [4] when chronic unilateral pyelonephritis is produced in rats by partial ureteral constriction and intravenous injection of Escherichia coli. It also develops in rats after unilateral nephrectomy and x-irradiation of the explanted remaining kidney,[5] or after unilateral nephrectomy and figure-of-eight ligatures of the remaining kidney.[6] It is more certain to do so if the animals are also given desoxycorticosterone acetate.[7] It occurs in about one-third of rats with a simple unilateral nephrectomy when they are given desoxycorticosterone acetate plus saline for a few weeks.[8] Many such animals may lose weight and look "toxic." [7] This type of hypertension is relieved by placing the animals in parabiosis with saline-fed normal rats.[9] The hypertension produced by total nephrectomy in one of a pair of parabiotic rats is relieved by adrenalectomy but then may be restored by desoxycorticosterone acetate, particularly if implanted in the nephrectomized member.[10] The administration of ascorbic acid also is said to moderate this type of renal hypertension, but not in adrenalectomized animals,[11] in which it develops, provided satisfactory nutrition is maintained for weeks with high sodium chloride intake.[12] A low protein diet will moderate the hypertension in subtotally nephrectomized rats, but the administration of corticotropin (ACTH) or the production of hypothyroidism will offset this

3. Fanconi, G.; Ruegg, T., and Dieterle, E.: Die "benigne" pyelonephritische und postpyelonephritische Hypertension, Helvet. paediat. acta **6**:281 (Aug.) 1951.

4. Spitznagel, J. E., and Schroeder, H. A.: Experimental Pyelonephritis and Hypertension in Rats, Proc. Soc. Exper. Biol. & Med. **77**:762 (Aug.) 1951.

5. Zollinger, H. U.: Hypertonie nach experimenteller Röntgenbestrahlung einer Niere bei Ratten, Schweiz. Ztschr. allg. Path. **14**:366 1951.

6. Rather, L. J.: The Pathogenesis of Hypertension Induced by Renal Constriction, J. Exper. Med. **92**:59 (July) 1950.

7. Freed, S. C.; Friedman, M., and Rosenman, R. H.: A Simple Method for Production of DCA Hypertension in Rats, Proc. Soc. Exper. Biol. & Med. **77**:732-733 (Aug.) 1951.

8. Friedman, S. M.; Friedman, C. L., and Nakashima, M.: Sustained Hypertension Following the Administration of Desoxycorticosterone Acetate (Adrenocortical Preparation), J. Exper. Med. **93**:361 (April) 1951.

9. Masson, G. M. C.; Corcoran, A. C., and Page, I. H.: Rôle du rein dans l'hypertension expérimentale chez le rat, Rev. canad. biol. **10**:309 (Oct.) 1951.

10. Ledingham, J. M.: The Nature of the Hypertension Occurring in the Nephrectomized Parabiotic Rat, Clin. Sc. **10**:423 (Nov.) 1951.

11. Heroux, O., and Dugal, L. P.: Effet de l'acide ascorbique sur l'hypertension provoquée par l'acétate de désoxycorticostérone, Rev. canad. biol. **10**:123, 1951.

12. Knowlton, A .I.; Loeb, E. N.; Seegal, B. C.; Stoerk, H. C., and Berg, J. L.: Development of Hypertension in the Adrenalectomiezd Nephritic Rat Maintained on NaCl, Proc. Soc. Exper. Biol. & Med. **74**:661 (Aug.) 1950. Barrell, G.: Über den Zeitpunkt des Blutdruckansteiges und die Bedeutung der Nebennieren bei experimenteller renaler Hypertonie, Helvet. med. acta **17**:599 (Dec.) 1950.

effect.[13] Exposure to cold will also offset the moderating effect of low protein and even of hypophysectomy on this type of hypertension.[13]

In weanling rats on a choline-deficient diet renal subcapsular bleeding develops and if the animals are transferred to a stock diet they may recover, only later to develop hypertension.[14] The hypertension may be prevented or relieved by removing proteins or NaCl from the diet or by renal decapsulation but may then be restored by administration of corticotropin.[15] Rats made hypertensive by renal capsulation with cellulose acetate have a further increase in blood pressure when given desoxycorticosterone acetate and saline.[16]

In rabbits made hypertensive by unilateral nephrectomy and constriction of the remaining renal artery, removal of the constriction relieves the hypertension within one day unless it has existed for weeks, in which case several days may be required to restore normotension.[17] Hypertension due to constriction (clipping) of one renal artery in rats persists in half the animals after removal of the constricting clip but is relieved in that half by then removing the untouched kidney. It persists after removal of both kidneys.[18] Surgical reduction of hepatic (particularly portal) blood flow sufficient to produce fatty infiltration of liver cells causes a delayed decrease of blood pressure in Goldblatt hypertensive dogs.[19] Moreover, inferior caval blood of dogs with a similar hypertension has a local vasoconstrictor effect early but not late after the production of the hypertension.[20] Similar results are obtained by dialysis, which yields a pressor substance resembling angiotonin (hypertensin).[21] A chronic (two weeks) constant hypertension may be produced in rabbits by continuous intravenous infusion of renin.[22] The hypertrophy of the juxtaglomerular apparatus of Goormaghtigh is seen in humans, as in animals, only with recently developed hypertension.[23]

13. Handler, P., and Bernheim, F.: Effects of Caloric Restriction, Salt Restriction, and Role of Pituitary and Adrenal Glands in Experimental Renal Hypertension, Am. J. Physiol. **166**:528 (Sept.) 1951.

14. Handler, P., and Bernheim, F.: Influence of Dietary Factors on Hypertension Induced by Choline Deficiency, Am. J. Physiol. **162**:189 (July) 1950. Moses, C., Longabauch, G. M., and George, R. S.: Production of Hypertension Following Choline Deficiency in Weanling Rats, Proc. Soc. Exper. Biol. & Med. **75**:660 (Dec.) 1950.

15. Handler, P., and Bernheim, F.: Effect of Renal Decapsulation on Hypertension Induced by Single Episode of Acute Choline Deficiency, Proc. Soc. Exper. Biol. & Med. **76**:338 (Feb.) 1951.

16. Gross, F.: Die Wirkung von DCA und Kochsalz auf den experimentellen Hochdruck der Ratte, Arch. internat. pharmacodyn. **81**:211 (Feb. 1) 1950.

17. Blackett, R. B., and Sellers, A. L.: The Effect of Removing the Constriction of the Renal Artery in Acute and Chronic Hypertension in the Rabbit, Clin. Sc. **10**:177 (May) 1951.

18. Floyer, M. A.: The Effect of Nephrectomy and Adrenalectomy upon the Blood Pressure in Hypertensive and Normotensive Rats, Clin. Sc. **10**:405 (Nov.) 1951.

19. Davis, L., and Tanturi, C. A.: Liver as a Factor in Experimental Renal Hypertension, A. M. A. Arch. Surg. **62**:325 (March) 1951.

20. Govaerts, P., and Verniory, A.: Recherches sur le pouvoir vasoconstricteur de sang cave au cours de l'hypertension rénale chez le chien, J. urol., Paris **51**:596, 1951.

21. Skeggs, L. T.; Kahn, J. R., and Shumway, N. P.: The Isolation of Hypertensin from the Circulating Blood of Normal Dogs with Experimental Renal Hypertension by Dialysis in an Artificial Kidney, Circulation **3**:384 (March) 1951.

22. Pickering, G. W.: Experimental Hypertension in the Rabbit: in Hypertension; a Symposium, edited by E. T. Bell, Minneapolis, University of Minnesota Press, 1951.

23. Goormaghtigh, N.: Le mesangium du flocculus glomérulaire: Ses reactions dans la glomérulonéphrite aiguë et les néphrites hypertensives, J. urol., Paris **57**:569, 1951.

No abnormalities can be demonstrated in the sodium and chloride excretion of Goldblatt hypertensive dogs.[24] The intrarenal tissue pressures of dogs are not related to their naturally occurring blood pressures.[25] The pH of the renal cortex of Goldblatt hypertensive dogs is more acid on the clamped than on the normal side,[26] and the renal cortex of renal (capsule) hypertensive rats and dogs and of hypertensive humans stains in an abnormally coarse fashion when incubated with tetrazolium.[27] In summary it may be said that renal disturbances undoubtedly may produce hypertension and are particularly liable to do so if salt and adrenal cortex salt-retaining hormones are added.

*Humoral Factors.*—The effect of desoxycorticosterone acetate in renal hypertension has just been mentioned. Worthy of note also are the facts that the administration of desoxycorticosterone acetate alone does not produce hypertension in rabbits [28] and does so only mildly in chicks,[29] occasionally in rats [30] and only in adult male dogs, not in bitches or in puppies.[31] In pairs of parabiotic rats the implantation of DCA pellets into one partner is reported to cause hypotension in it but hypertension in its partner.[32] The administration of vitamin E is said to reduce the pressure in desoxycorticosterone acetate hypertensive rats [30] while $NH_4Cl$ fails to do so, although $NH_4Cl$ does appear to inhibit the development of cardiovascular lesions.[33] Adrenalectomy or bilateral nephrectomy (with three day survival) does not relieve salt (2% sodium chloride for drinking water) hypertension in rats, although substitution of tap water does.[34] Potassium restriction prevents desoxycorticosterone acetate hypertension in rats, but excess potassium administration augments it.[35] Adrenalectomy and administration of desoxycorticosterone acetate lessen but do not abolish the preference of renal (capsule) hypertensive rats for

24. Stamler, J.; Hwang, W., and Kuramoto, K.: Renal Clearances of Sodium and Chloride in Goldblatt Hypertensive Dogs, Am. J. Physiol. **165**:328 (May) 1951.

25. Montgomery, A. V.; Davis, J. C., Jr.; Prime, J. M., and Swann, H. G.: The Intrarenal Pressure: Its Relation to Age, Weight, Blood Pressure and Sex, J. Exper. Med. **92**:637 (Dec.) 1950.

26. Olsen, N. S., and Schroeder, H. A.: Oxygen Tension and pH of Renal Cortex in Acute Ischemia and Chronic Hypertension, Am. J. Physiol. **163**:181 (Oct.) 1950.

27. Zweifach, B. W.; Black, M. M., and Shorr, E.: Histochemical Alterations Revealed by Tetrazolium Chloride in Hypertensive Kidneys in Relation to Renal VEM Mechanisms, Proc. Soc. Exper. Biol. & Med. **74**:848 (Aug.) 1950.

28. Verniory, A.: Action de l'acétate de désoxycorticostérone sur la pression artérielle du lapin, Arch. internat. Pharmacodyn. **85**:451 (Feb.) 1951.

29. Stamler, J.; Pick, R., and Katz, L. N.: Effects of Desoxycorticosterone Acetate on Cholesteremia, Blood Pressure and Atherogenesis in Chicks, Circulation **4**:262 (Aug.) 1951.

30. Allardyce, J.; Salter, J., and Rexon, R.: Experimental Hypertension, Am. J. Physiol. **164**:68 (Jan.) 1951.

31. deMuro, P., and Rovinsky, P.: The Role of Sex in the Hypertensive Action of Desoxycorticosterone Acetate, Acta med. scandinav. 141-70, 1951.

32. Hall, C. E., and Hall, O.: Hypertensive Disease Produced by Desoxycorticosterone Acetate in Parabiotic Rats, A. M. A. Arch. Path. **51**:249 (March) 1951.

33. Hall, C. E.; Hall, O., and Pinkston, D. A.: Desoxycorticosterone Hypertension and Ammonium Chloride, Proc. Soc. Exper. Biol. & Med. **75**:446 (Nov.) 1950.

34. Brandt, W. L.; Dubin, W. M., and Sapirstein, L. A.: Studies on Salt Hypertension: Effects of Adrenalectomy and Nephrectomy, Am. J. Physiol. **146**:73 (Jan.) 1951.

35. Rosenman, R. H.; Freed, S. C., and Friedman, M.: Effect of Variation of Potassium Intake on Pressor Activity of Desoxycorticosterone, Proc. Soc. Exper. Biol. & Med. **78**:77 (Oct.) 1951.

reduced dietary sodium.[36] Young rats prefer more dietary sodium and less water than old rats.[37] The enlarged adrenals of renal hypertensive rats differ from the enlarged adrenals of corticotropin-treated rats in having a relative increase in medullary size, whereas the corticotropin-treated rats have a relative decrease in medullary size.[38] Adrenal ischemia has not been confirmed as a possible pathogenic factor in experimental hypertension.[39]

Turning to human hypertension with respect to the sodium-chloride-adrenal-cortex relationships, a slight but statistically significant elevation of serum sodium is reported in patients with uncomplicated hypertension.[40] However, no abnormalities in sweat sodium are found in patients with essential hypertension,[41] although in menopausal women with central obesity, hypertension, and other signs mildly suggesting hyperadrenocorticism, sweat sodium is reported to be abnormally low.[42] A most significant human experiment in this connection is the demonstration that a prehypertensive (familial hypertensive) person with normal blood pressure and no evidence of vascular disease may have an abnormal elevation of pressure associated with an abnormal retention of sodium when given desoxycorticosterone acetate but an abnormally small loss of weight when given a sodium-free diet.[43] One cannot help speculating upon the role of salt, water, and extracellular and intracellular fluid in hypertension, since so many suggestions of their importance are found in clinical and experimental data.[44]

The role of numerous other humoral substances in hypertension continues to be discussed.[45] However, no new humoral substances have been proposed as pathogenic since June, 1950. The ones most often discussed are the pressor amines,[46]

36. Tosteson, D. C.; Depriez, A. I. C.; Abrams, M.; Gottschalk, C. W., and Landis, E. M.: Effects of Adrenalectomy, Desoxycorticosterone Acetate and Increased Fluid Intake on Intake of Sodium Chloride and Bicarbonate by Hypertensive and Normal Rats, Am. J. Physiol. **164**: 369 (Feb.) 1951.

37. Lucie, R.; Causeret, J.; Gaurel, M., and Szyman, S. K.: Comportement du jeune rat normal auquel on donne le choix entre de l'eau pure et une solution peu concentrée de chlorure de sodium, Physiol., Paris **42**:447, 1950.

38. Rather, L. J.: Differences of Cortical Medullary Ratio in the Adrenals of Normal Rats, Normal Rats Treated with ACTH, and Renal Hypertensive Rats, Proc. Soc. Exper. Biol. & Med. **77**:651 (Aug.) 1951.

39. Cier, J. F.: A propos de l'ischémie surrénale comme facteur d'hypertension, Compt. rend. Soc. biol. **144**:533 (April) 1950.

40. Holley, H. L.; Elliott, H. C., Jr., and Holland, C. M., Jr.: Serum Sodium Values in Essential Hypertension, Proc. Soc. Exper. Biol. & Med. **77**:561 (July) 1951.

41. Eisenberg, S.; Buie, R., Jr., and Tobian, L., Jr.: Adrenal Cortical Function in Essential Hypertension: A Study of Sweat Sodium Concentration, Am. J. M. Sc. **220**:287 (Sept.) 1950.

42. Davies, D. F., and Clark, H. E.: A Hypertensive Syndrome with Relative Adrenal Cortical Overactivity, Circulation **2**:494 (Oct.) 1950.

43. Perera, G. A.: Altered Metabolic Response Prior to the Development of Hypertensive Vascular Disease, Am. Heart J. **42**:308 (Aug.) 1951.

44. Braun, E.; Menendez, S.; Bruie, R., and Tobian, L.: L'hypertension et Léclampsie au cours de l'insuffisance rénale aiguë, Acta clin. belg. **6**:421, 1951. Vanatta, J. C.: Biochemical Disturbances in Hypertension, Letter to the Editor, J. A. M. A. **147**:893 (Oct. 27) 1951.

45. Schroeder, H. A.: The Pathogenesis of Hypertension, Am. J. M. Sc. **10**:189 (Feb.) 1951.

46. Rall, N., and Lepeschkin, E.: Biochemical Versus Hemodynamic Factors in the Origin of "Hypertensive" Heart Disease, Acta med. scandinav. **138**:81, 1950. Olsen, N. S.; Schroeder, H. A., and Menhard, E. M.: Effect of Certain Amines on the Blood Pressure of Normotensive and Hypertensive Rats, Proc. Soc. Exper. Biol. & Med. **74**:581-583 (July) 1950.

renin-angiotonin,[47] pherentasin,[48] and vasoexcitor materials (VEM).[49] The possible role of antidiuretic hormone in essential hypertension also is mentioned.[50] The multiplicity of these various humoral pressor substances reported, on the one hand, and the lack of independent confirmation of their importance, on the other, leave considerable confusion as to their roles in human essential hypertension. Only in the hypertension of pheochromocytoma do the pressor amines, epinephrine and arterenol (norepinephrine), seem definitely pathogenic.[51] Patients with essential hypertension before sympathectomy respond normally to the pressor effects of epinephrine and arterenol except that their pulse rates do not slow normally, but after lumbodorsal sympathectomy both blood pressure and pulse rate responses are essentially normal.[52]

*Neurogenic Factors.*—This section will be divided into two parts: (1) peripheral neurogenic factors and (2) central neurogenic (including psychogenic) factors.

Peripheral Neurogenic Factors: By this term is implied those neural mechanisms in hypertension which presumably operate essentially independently of central nervous system, and particularly cerebral cortex, activity. They include the effects of sympathetic nerve stimulation and the classic carotid sinus and aortic depressor nerve excision. The most exciting new work in this field is that on the effects of various pressor substances (*l*-epinephrine, *l*-arterenol and *β*-hypophamine [pitressin]) and depressor substances (papaverine, KCl, priscoline, and adrenolytic drugs) applied locally on the carotid sinus of dogs.[53] Local application of pressor

47. Kahn, J. R.; Skeggs, L. T., and Shumway, N. P.: The Isolation of Hypertensin from the Circulating Blood of Dogs by Dialysis in an Artificial Kidney, Circulation **2**:363 (Sept.) 1950.

48. Schroeder, H. A., and Olsen, N. S.: Pressor Substances in Arterial Hypertension: II. Demonstration of Pherentasin, a Vasoactive Material Procured from Blood, J. Exper. Med. **92**:545 (Dec. 1) 1950. Olsen, N. S., and Schroeder, H. A.: Pressor Substances in Arterial Hypertension: III. Chemical Studies on Pherentasin, J. Exper. Med. **92**:561 (Dec. 1) 1950.

49. Shorr, E.: The Participation of Hepatorenal Factors in Experimental Renal Hypertension: in Hypertension; A Symposium, edited by E. T. Bell, Minneapolis, University of Minnesota Press, 1951, p. 79.

50. de Paiva, L. M.; Henriques, O. B.; Henriques, S. B., and do Valle, J. R.: Dosagem do hormônio antidiurético no sôro de pacientes com hipertensão arterial, An. paulist. med. e cir. **61**:132 (Feb.) 1951.

51. Pitcairn, D. M., and Youmans, W. B.: The Nature of Pressor Substances in Pheochromocytomas, Circulation **2**:505 (Oct.) 1950. Beyer, K. H.; Ross, C. A.; Wielbelhaus, V. D.; Waller, W. S., and Schuchardt, G. S.: Vasopressor Components of Pheochromocytomas, Ann. Int. Med. **35**:117 (July) 1951.

52. Judson, W. E.; Culbertson, J. W.; Tinsley, C. M.; Litter, J., and Wilkins, R. W.: The Comparative Effects of Small Intravenous Doses of Epinephrine upon Arterial Pressure and Pulse Rate in Normotensive Subjects and in Hypertensive Patients Before and After Thorocolumbar Sympathectomy, J. Clin. Invest. **29**:1405 (Oct.) 1950. Judson, W. E.; Epstein, F. H., and Wilkins, R. W.: The Comparative Effects of Small Intravenous Doses of l-Nor-Epinephrine upon Arterial Pressure and Pulse Rate in Normotensive Subjects and in Hypertensive Patients Before and After Thoracolumbar Sympathectomy, ibid. **29**:1414 (Oct.) 1950.

53. (*a*) Heymans, C., and van den Heuvel-Heymans, G.: Action of Drugs on Arterial Wall of Carotid Sinus and Blood Pressure (Preliminary Communication), Arch. internat. pharmacodyn. **83**:520 (Sept. 1) 1950. (*b*) Heymans, C.; de Vleeschhouwer, G. R., and van den Heuvel-Heymans, G.: Adrenolytic Drug and Action of Adrenaline and Noradrenaline on Carotid Sinus, ibid. **85**:188 (Jan. 1) 1951. (*c*) Heymans, C., and van den Heuvel-Heymans, G.: New Aspects of Blood Pressure Regulation, Circulation **4**:581 (Oct.) 1951.

substances on the carotid sinus causes a progressive and profound fall in arterial pressure, inhibition of the respiration, and a loss or a decrease of the normal pressor response to a lowering of blood pressure in the sinus. Section of the carotid sinus nerves then causes an immediate marked rise in arterial pressure. Local application of adrenolytic drugs reverses the effect of locally applied epinephrine or arterenol. Local application of vasodilators on the sinus induces a reflex rise in arterial pressure and increases the effects of a fall in pressure in the sinus. These experiments show that the local state of contraction (elasticity) of the sinus affects its reflex activity and that a decrease in this state may produce hypertension.[53a] The findings gain clinical support in the pathology observation that the elasticity of the carotid sinus apparently is inversely related to the age and the blood pressure of the patient, particularly in women. This inverse correlation is best in malignant hypertension and poorest in nephritis with hypertension.[54]

If dogs are made hypertensive by carotid sinus and aortic depressor denervation, arterial pressure rises markedly at first, but then collapses, with venous congestion and electrocardiographic evidence of acute myocardial insufficiency, from which the animal may either die or slowly recover, only to return to a labile hypertensive state. Apparently the myocardium cannot tolerate an acute severe hypertension such as that produced when a widespread denervation, including cutting the vagosympathetic trunk, is carried out at the same time but can tolerate an equally severe hypertension if it is produced gradually as by operating in several stages.[55] Cardiac sympathectomy may abolish cardioacceleration in such dogs but causes only a slight fall in arterial pressure.[56] Neurogenic hypertension is reported to occur in the dog when a branch of the pulmonary artery or veins is clamped.[57] The importance of peripheral neurogenic mechanisms in maintaining hypertension in many patients is suggested by the falls in pressure ("floors") produced by tetraethylammonium chloride and spinal anaesthesia[58] in essential as contrasted with "renal" or "humoral" hypertension occurring naturally or as a result of the administration of corticotropin.[59]

Central Neurogenic Factors: There has been a renewal of interest in the brain with respect to hypertension. Techniques for perfusing isolated heads of dogs have been reviewed and revised, and the effects of various drugs have been studied.[60]

54. Asteroth, H., and Kreuzinger, H.: Dehnungsstudien am isolierten Sinus caroticus von verstorbenen Normotonikern und Hypertonikern, Ztschr. Kreislaufforsch. **40**:11 (Jan.) 1951.

55. Jourdan, F., and Collet, A.: Evolution de la pression artérielle chez le chien après la suppression de ses mechanismes nerveux régulateurs, J. physiol., Paris **43**:149, 1951.

56. McCubbin, J. W., and Page, I. H.: Role of Cardioacceleration in Chronic Experimental Neurogenic Hypertension, Am. J. Physiol. **166**:12 (July) 1951.

57. Donnet, V.; Zwirn, P., and Ardisson, R.: Signification de l'hypertension arterielle provoquée par l'occlusion d'une branche de l'artère pulmonaire chez le chien, Compt. rend. Soc. biol. **144**:1534 (Nov.) 1950.

58. Brust, A. A.; Reiser, M. F., and Ferris, E. B., Jr.: Evaluation of Neurogenic Control of Blood Pressure in Hypertension with Tetraethylammonium Chloride and Spinal Anesthesia, J. Clin. Invest. **30**:925 (Sept.) 1951.

59. Brust, A. A.; Ransohoff, W., and Reiser, M. F.: Blood Pressure Responses to ACTH and Cortisone in Normotensive and Hypertensive Subjects in the Resting State and During Autonomic Blockade with Tetraethylammonium Chloride: Proceedings of the Forty-Third Annual Meetings, American Society for Clinical Investigation, abstracted, J. Clin. Invest. **30**:630 (June) 1951.

In general, pressor drugs isolated to the head cause systemic hypotension and depressor drugs cause hypertension in a manner similar to but independent of the carotid sinus effects mentioned already. Changing the perfusing pressure mechanically has no effect upon the systemic arterial pressure in such animals. Veratrum viride in the isolated head causes a marked fall in pressure [60c] and also blocks the effects of the other drugs injected into the head.[60c] Stimulation of the central end of the vagus in such animals elicits the liberation of a pressor substance into the blood.[61] This pressor substance may be released from the arterial walls [61a] but appears to be distinct from epinephrine, pitressin, renin, or angiotonin. It resembles arterenol [61a] and its activity is enhanced by tetraethylammonium chloride and inhibited by l-hydrazinophthalazine.[61b]

Surgically induced cerebral ischemia in dogs combined with fourth ventricle stimulation by a diathermy-heated embedded wire causes a neurogenic hypertension in two-thirds of the animals for 2 to 10 months.[62] Electrical stimulation of the hypothalamus of cats is reported to raise the arterial pressure and to cause contraction of the nictitating membrane, both of which reactions are said to be abolished by tetraethylammonium.[63] Another report states that tetraethylammonium does not block the rise in blood pressure induced by electrical stimulation of the lateral thalamic region but, rather, delays this rise and the subsequent fall on stopping the stimulation.[64] The occurrence of hypertension in poliomyelitis and in trigeminal neuralgia may be related to central nervous system lesions or ischemia, but also may arise as a result of the stressful psychogenic effects of pain and fear of paralysis.[65] Hypertension in patients with intermittent claudication also may be due in part to factors other than the pain.[66] The cold pressor test and the sedation (sodium

60. (*a*) Taylor, R. D., and Page, I. H.: Peripheral Vasomotor Effects of Adrenaline and Noradrenaline Acting upon the Isolated Perfused Central Nervous System, Circulation **4**:563 (Oct.) 1951; (*b*) Further Studies of the Cerebral Chemoreceptor Buffers as Influenced by Vasoconstrictor and Vasodilator Drugs and Veratrum Viride, ibid. **4**:184 (Aug.) 1951. (*c*) Swiss, E. D.; Simon, H., and Stutzman, J. W.: The Site of Cardiovascular Action of Hypotensive Veratrum Derivatives, Federation Proc. **10**: No. 1, Pt. 1 (March) 1951.

61. (*a*) Jiménez Diaz, C.; de la Barreda, P.; Souto Candeira, J., and Alcalá, R.: Additional Studies on the Function of the Vascular Wall in Arterial Pressure Regulation, Bull. Inst. M. Res. **3**:131 (July-Sept.) 1950. (*b*) Taylor, R. D.; Page, I. H., and Corcoran, A. C.: A Hormonal Neurogenic Vasopressor Mechanism, A. M. A. Arch. Int. Med. **88**:1 (July) 1951.

62. Taylor, R. D., and Page, I. H.: Production of Prolonged Arterial Hypertension in Dogs by Chronic Stimulation of the Nervous System: Exploration of the Mechanism of Hypertension Accompanying Increased Intracranial Pressure, Circulation **3**:551 (April) 1951.

63. Conley, C., and Gellhorn, E.: The Action of Tetraethylammoniumchloride TEA on the Stimulation of the Hypothalamus and on the Action of Adrenalin and Nor-Adrenaline, Acta neuroveg. **2**:284, 1951.

64. Bartorelli, C., and Zanchetti, A.: Meccanismo dell'ipertensione ipotalamica sperimentale: Effetto della somministrazione di 933 F e bromuro di tetraetilammonio, Folia cardiol. (Supp.) **9**:9, 1951.

65. McDowell, F. H., and Plum, F.: Arterial Hypertension Associated with Acute Anterior Poliomyelitis, New England J. Med. **245**:241 (Aug. 16) 1951. Döring, G., and Magun, R.: Trigeminusneuralgie und Arteriohypertonie, Deutsche Ztschr. Nervenh. **166**:196, 1951. Sennett, L. W.; Perlstein, M. A.; Andelman, M. B.; Barnett, H. E., and Hosephy, H.: Hypertension in Poliomyelitis with Respiratory Paralysis: Report of Protracted Case with Necropsy Findings, Pediatrics **7**:529 (April) 1951.

66. Malinow, M. R.; Moia, B.; Otero, E.; e Rosenbaum, M.: A occorência de hipertensão paroxistica em facientes com claudicacao intermittente, Arq. clín. **12**:98, 1951.

bromide) depressor test are advocated for selecting "neurogenic hypertensives."[67] but are said to show no real differences in patients with known nephritis and those with assumed essential hypertension.[68]

Psychogenic Factors: Interest in and efforts at clarifying the role of psychological factors in human hypertension remain largely on the conversational, descriptive level.[69] However, the generally recognized importance of emotional stress as a potent pressor stimulus and an aggravating factor in the course of hypertension has been better documented.[70] No specific personality structure is apparent in hypertension,[71] although anxiety, perfectionistic strivings, and a fear of expressing aggression are prominent. Psychotherapy usually improves symptoms and may lower blood pressure. In one patient psychotherapy was ineffectual until after a prefrontal lobotomy, which appeared to make the patient amenable to psychotherapy.[72] "Hallucinatory psychosis," even of long standing, very often is associated with hypertension.[73] One such patient is said to have been cured by prefrontal lobotomy.[74]

Efforts at measuring discrete hemodynamic and renal functional changes in relation to psychological factors are most interesting and promising.[75] During emotional stress hypertensive patients apparently have a greater degree of renal vasoconstriction than do normotensive subjects.[75b]

67. Saracoglu, K.: Die Beurteilung der Hypertonie durch einen gekreuzten Test, Ztschr. Kreislaufforsch. **40**:422 (July) 1951.

68. Beretta, A.; Dal Palù, C., and Rizzi, R.: Sulla reattività tensiva arteriosa, Folia cardiol. **10**:3 (Feb.) 1951.

69. Binger, C.: On So-Called Psychogenic Influences in Essential Hypertension, Psychosom. Med. **13**:273 (Sept.-Oct.) 1951.

70. Reiser, M. F.; Brust, A. A., and Ferris, E. B.: Life Situations, Emotions, and the Course of Patients with Arterial Hypertension, Psychosom. Med. **13**:133 (May-June) 1951. Reiser, M. F.; Rosenbaum, M., and Ferris, E. B.: Psychologic Mechanisms in Malignant Hypertension, ibid. **13**:147 (May-June) 1951.

71. Footnotes 69 and 70. Palmer, R. S.: Psyche and Blood Pressure: 100 Mental Stress Tests and 50 Personality Surveys in Patients with Essential Hypertension, J. A. M. A. **144**:295 (Sept. 23) 1950. Tucker, W. I.: Psychiatric Factors in Essential Hypertension: Followup Study of 74 Cases, New England J. Med. **243**:211 (Aug. 10) 1950. Lowy, S.: A Few Notes on Hypertension, Psychotherapy **5**:362 (July) 1951. Altschule, M. D.: Emotion and the Circulation, Circulation **3**:444 (March) 1951.

72. Groen, J.: Malignant Hypertension Treated with Prefrontal Lobotomy and Psychotherapy, Nederl. tijdschr. geneesk. **95**:2336 (Aug. 11) 1951.

73. Hyvert, M., and Fagard, H.: Fréquence de l'hypertension artérielle chez les malades atteints de psychose hallucinatoire, Annales médico-psycholog. **109**:608, 1951.

74. Petit-Dutaillis, D.; Borel, A.; Messimy, R., and Bouvet, M.: Psychose hallucinatoire chronique avec hypertension artérielle: Guérison des troubles psychiques et de l'hypertension après lobotomie préfrontale bilatérale, Rev. neurol. **84**:154 (Feb.) 1951.

75. (*a*) Wolf, S., and Wolff, H. G.: A Summary of Experimental Evidence Relating Life Stress to the Pathogenesis of Essential Hypertension in Man: in Hypertension; a Symposium, edited by E. T. Bell, Minneapolis, University of Minnesota Press, 1951, p. 288. (*b*) Pfeiffer, J. B., Jr., and Wolff, H. G.: Studies in Renal Circulation During Periods of Life Stress and Accompanying Emotional Reactions in Subjects With and Without Essential Hypertension: Observations on the Role of Neural Activity in Regulation of Renal Blood Flow, J. Clin. Invest. **29**:1227 (Sept.) 1950.

*Hereditary Factors.*—Little work is being done on this most probable of all factors in the production of essential hypertension in man. There seems little doubt that when both parents have hypertension there is a high familial tendency toward the disease extending to the third and fourth generations.[76] This tendency is being examined in an interesting study of medical students before and after the appearance of hypertension, with reference to hyperreactivity, pulse rate responses, and salt metabolism.[77] Climatic or dietary factors apparently do not determine the incidence of hypertension in racial groups.[78]

## PATHOLOGIC PHYSIOLOGY

The pathologic physiology of the circulation in essential hypertension has been recently reviewed.[79] The most obvious hemodynamic abnormality remains, as before, generalized increase in peripheral vascular resistance, but this apparently is not due to a continuous direct sympathetic nervous hyperactivity. The hepatic portal circuit has been shown to participate in this characteristic of the general circulation in hypertension,[80] as does the fingertip.[81] While cerebral vascular resistance is increased in essential hypertension, it may be partially reduced by tilting upright and by sympathectomy.[82]

Considerable interest is still taken in the matter of "hyperreactivity" of the blood pressure of hypertensive and "prehypertensive" patients under various types of stimulation.[83] It is still not clear whether these responses should be graded in milli-

76. Ayman, D.: Hereditary and Constitutional Factors in Essential Hypertension in Man: in A Symposium on Essential Hypertension: An Epidemiologic Approach, Boston, The Commonwealth of Massachusetts, 1951, p. 234.

77. Thomas, C. B.: Observations on Some Possible Precursors of Essential Hypertension and Coronary Artery Disease, Bull. Johns Hopkins Hosp. **89**:419 (Dec.) 1951.

78. Suarez, R. M.: Incidence of Hypertension in Puerto Rico, Ann. Int. Med. **33**:346 (July) 1950.

79. Wilkins, R. W.: Physiological Investigations of Essential Hypertension in Man: in A Symposium on Essential Hypertension: An Epidemiological Approach, The Commonwealth of Massachusetts, Boston, 1951, p. 94.

80. Culbertson, J. W.; Wilkins, R. W.; Ingelfinger, F. J., and Bradley, S. E.: The Effect of the Upright Posture upon Hepatic Blood Flow in Normotensive and Hypertensive Subjects, J. Clin. Invest. **30**:305 (March) 1951. Wilkins, R. W.; Culbertson, J. W., and Ingelfinger, F. J.: The Effect of Splanchnic Sympathectomy in Hypertensive Patients upon Estimated Hepatic Blood Flow in the Upright as Contrasted with the Horizontal Position, ibid. **30**:312 (March) 1951.

81. Mendlowitz, M.: Digital Vascular Resistance in Normal, Polycythemic and Hypertensive States, Circulation **3**:694 (May) 1951.

82. Hafkenschiel, J. H.; Crumpton, C. W.; Shenkin, H. A.; Moyer, J. H.; Zintel, H. A.; Wendel, H., and Jeffers, W. A.: The Effects of 20 Degree Head-Up Tilt upon the Cerebral Circulation of Patients with Arterial Hypertension Before and After Sympathectomy, J. Clin. Invest. **30**:793 (Aug.) 1951.

83. Smithwick, R. H., and Robertson, C. W.: Phenomenon of Hyperreactivity: Definition and Illustrations, Angiology **2**:143, (June) 1951. Hines, E. A., Jr.: Vascular Reactivity and Hypertensive Disease: in Hypertension: A Symposium, edited by E. T. Bell, Minneapolis, University of Minnesota Press, 1951, p. 331. Smithwick, R. H., and Robertson, C. W.: The Phenomenon of Hyperreactivity: Definition and Illustrations: in A Symposium on Essential Hypertension: An Epidemiologic Approach, Boston, The Commonwealth of Massachusetts, 1951, p. 239. Hines, E. A., Jr.: The Significance of Hyperreactivity in the Natural History of Essential Hypertension: in A Symposium on Essential Hypertension: An Epidemiologic Approach, Boston, The Commonwealth of Massachusetts, 1951, p. 256.

meters of mercury or in the percentage of rise of blood pressure and, therefore, just what constitutes "hyperreactivity." Nevertheless, variability and lability of blood pressure and pulse rate are generally regarded as frequent in young hypertensives, and may be a "prehypertensive" sign of significance.[84] Further studies on familial tendencies toward these responses are needed.

A good bit of experimental work has been done on the blood pressure responses of hypertensive animals to various vasoconstrictor and vasodilator substances in efforts to assess "vascular reactivity." Chronic hypertensive animals react in a manner different from that of animals with acutely produced hypertension. For example, tetraethylammonium chloride always lowers the pressure more in chronic than in acutely produced hypertension, in which it may actually raise the pressure.[85] Such rises in pressure may be due in part to modification of homeostatic reflexes by tetraethylammonium chloride but are also due in part to alteration of the peripheral motor effects of pressor substances by the drug.[86] Chronic neurogenic-hypertensive animals have exaggerated depressor responses to tetraethylammonium chloride, veratramine, $CO_2$, and other depressor substances, in contrast to chronic renal hypertensives, who have normal responses.[87] Tetraethylammonium chloride reduces the depressor response to veratramine in chronic neurogenic hypertension.[87b] $CO_2$ produces refractoriness to vasoactive drugs but not in totally sympathectomized animals.[87c] Studies of vascular resistance in various regions in chronic hypertensive animals indicate that it is most increased in the mesenteric bed.[88]

### PATHOLOGIC ANATOMY

In a large series of autopsies, renal pathology is found four times as frequently in the cases with hypertension as in those with none. Of the hypertensives, 7.5% have unilateral renal disease.[89] Renal impairment and early mortality are clearly correlated with the degree of the hypertension.[90] Aberrant renal arteries appear to be definitely more frequent in hypertensive than in normotensive patients studied at necropsy.[91] Of all patients with hypertension coming to autopsy, 32% die of

84. Thomas.[77] Vančura, A.: On Transient Hypertension in Young Subjects, Cardiologia **16**:124, 1950.

85. Page, I. H., and McCubbin, J.: The Pattern of Vascular Reactivity in Experimental Hypertension of Varied Origin, Circulation **4**:70 (July) 1951.

86. St. Clair, W. R., and Stone, C. A.: Potentiating Effect of Tetraethylammonium on Pressor Response to Epinephrine and Nor-Epinephrine, Proc. Soc. Exper. Biol. & Med. **77**:542 (July) 1951.

87. (*a*) Page and McCubbin.[85] (*b*) McCubbin, J. W., and Page, I. H.: Effect of Veratramine on Arterial Pressure and Heart Rate in Normal and Hypertensive Dogs, Am. J. Physiol. **167**:714 (Dec.) 1951. (*c*) Page, I. H., and Olmstead, A. B.: The Influence of Respiratory Gas Mixtures on Arterial Pressure and Vascular Reactivity in "Normal" and Hypertensive Dogs, Circulation **3**:801 (June) 1951.

88. Williams, A. H., and Schroeder, H. A.: Regional Vasomotor Tone in Normotensive and Hypertensive Dogs, Circulation **4**:706 (Nov.) 1951.

89. Bretschger, E.: Die absolute und relative Häufigkeit der renalen Hypertonie und die ihr zugrunde liegenden Nierenerkrankungen (Statistische Untersuchungen an 3142 Sektionen), Cardiologia **19**:182, 1951.

90. Smith, D. E.; Odel, H. M., and Kernohan, J. W.: Causes of Death in Hypertension, Am. J. Med. **9**:516 (Oct.) 1950.

91. Marshall, A. G.: Aberrant Renal Arteries and Hypertension, Lancet **2**:701 (Oct. 20) 1951.

cerebral vascular disease, 27% die of congestive failure, 11% die of coronary occlusion, 6% die of uremia, and 24% die of incidental causes.[92] Organic cerebral vascular disease (hyaline degeneration and necrosing arteritis) appears to be the fundamental lesion underlying cerebral symptoms and signs in hypertension.[93] Careful histological examination of the diencephalon in five cases of hypertension revealed no abnormalities.[94] The aorta is definitely elongated in hypertension.[95]

### COURSE AND PROGNOSIS

Transient hypertension in otherwise normal young people probably represents an early sign of hypertensive disease.[84] Since the incidence of hypertension increases with age, limits of normal blood pressure should probably be revised upward for older age groups.[96] It is generally agreed that the blood pressure alone is not adequate for diagnosis or prognosis. Borderline readings should signal the advisability of further study of the patient for possible correlated abnormalities.[96] Hypertension appearing after age 55 is associated with renal arteriosclerosis in only 32% of patients, as contrasted with 72% of patients with hypertension appearing before age 55, suggesting that it may be a manifestation of a different disease in the two groups.[97] When unselected patients are followed from onset of hypertension to death, it is found that the average age at onset is 32 and at death 51.[98]

Vascular disease, whether manifested by cardiac enlargement, electrocardiographic abnormalities, renal abnormalities, or encephalopathy, is a serious prognostic sign.[99] Systolic and diastolic blood pressure levels, sex, and retinopathy are also important, but the rate of progression of these several signs is the most important of all.[100] Overweight in the presence of hypertensive vascular disease is a poor prognostic sign.[101] Regression of electrocardiographic abnormalities (which may occur with weight loss) is not a reliable indication of improvement of hypertensive disease.[102] However, regression of papilledema and severe retinopathy is a favor-

92. Belton, R. R.: Pathologisch—anatomische Auswertung von 481 Fällen mit Hypertonie, Cardiologia **19**:108, 1951.

93. Smith, S. A.: Cerebral States in Hypertension, Proc. Roy. Australasian Coll. Physicians **6**:13 (Jan.) 1951.

94. Wehrle, J.: Histologische Untersuchungen des Zwischenhirns bei genuiner Hypertonie, Beitr. path. Anat. **3**:381, 1951.

95. Dotter, C. H.; Roberts, D. J., Jr., and Steinberg, I.: Aortic Length: Angiocardiographic Measurements, Circulation **2**:915 (Dec.) 1950.

96. Master, A. M.; Dublin, L. I., and Marks, H. H.: The Normal Blood Pressure Range and Its Clinical Implications, J. A. M. A. **143**:1464 (Aug. 26) 1950.

97. Krane, S. M., and Perera, G. A.: Hypertension in Older Age Groups, Ann. Int. Med. **34**:1017 (April) 1951.

98. Perera, G. A.: Life History of 100 Patients with Hypertensive Vascular Disease, Am. Heart J. **42**:421 (Sept.) 1951.

99. Hetzel, B. S.: Some Aspects of the Natural History of Hypertensive Vascular Disease, M. J. Australia **2**:22 (Aug.) 1951.

100. Griep, A. H.; Barry, G. R.; Hall, W. C., and Hoobler, S. W.: Prognosis in Arterial Hypertension: Report on 117 Patients Under 53 Years of Age Followed 8 to 10 Years, Am. J. M. Sc. **221**:239 (March) 1951.

101. Ross, P. S.: Hypertension and Arterial Disease, Ohio M. J. **47**:639 (July) 1951.

102. Palmer, R. S.: "Improvement" in the Hypertensive Pattern of the Electrocardiogram, Ann. Int. Med. **34**:712 (March) 1951.

able prognostic sign and may occur spontaneously as well as after treatment.[103] Mild retinopathy or none at all may occur in 70% of patients with established hypertension, but this does not necessarily indicate a favorable prognosis,[104] although marked retinopathy, particularly papilledema, does indicate a poor prognosis.[105] Hypertensive patients, therefore, cannot be classified solely on the basis of their eyegrounds. The conjunctival vessels are said to show typical abnormalities in hypertensive patients.[106] Ballistocardiograms are abnormal in hypertension[107] and fail to increase in size normally after exercise.[108] Hypertension does not appear to be more frequent in patients with mitral stenosis than in other people of the same age and sex.[109] Hypertension may appear in patients with cardiac disease with the onset of congestive failure and recede with recompensation after treatment.[110]

### HYPERTENSION IN PREGNANCY

The differentiation of primary renal disease, essential hypertension in pregnancy, and toxemia of pregnancy, or combinations of these, is important[111] and is being attempted through the use of tests for serum gonadotropins, water excretion, and

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103. (*a*) Keith, N. M., and Wagener, H. P.: Recession of Neuroretinopathy During the Course of Malignant Hypertension: Its Occurrence in 15 Patients Who Did Not Receive Directed Therapy, A. M. A. Arch. Int. Med. **87**:25 (Jan.) 1951. (*b*) Schottstaedt, M. F., and Sokolow, M.: Natural History and Course of Malignant Hypertension, Am. J. Med. **11**:626 (Nov.) 1951.

104. Vogelius, H., and Bechgaard, B.: Ophthalmoscopical Appearance of Fundus Oculi in Elderly Persons with Arterio-Sclerosis and Normal Blood Pressures, Brit. J. Ophth. **34**:404 (July) 1950. Bechgaard, P.; Porsaa, K., and Vogelius, H.: Ophthalmological Investigations of 500 Persons with Hypertension of Long Duration, ibid. **34**:409 (July) 1950.

105. Schottstaedt and Sokolow.[103b] Thiel, R.: Augenhintergrundsveränderungen bei arterieller Hypertonie und Nierenkrankheiten, Deutsche med. Wchnschr. **75**:1495 (Nov. 10) 1950.

106. Lee, R. E., and Holze, E. A.: Peripheral Vascular Hemodynamics in Bulbar Conjunctiva of Subjects with Hypertensive Vascular Disease, J. Clin. Invest. **30**:539 (June) 1951.

107. Jones, R. J., and Goulder, N. E.: An Empiric Approach to the Interpretation of the Low Frequency, Critically Damped Ballistocardiogram, Circulation **2**:756 (Nov.) 1950. Mandelbaum, H., and Mandelbaum, R. A.: Studies Utilizing the Portable Electromagnetic Ballistocardiograph: I. Abnormal HIJK Patterns in Hypertensive and Coronary Artery Heart Disease, ibid. **3**:663 (May) 1951. Williams, A. H., and Gropper, A. L.: Interrelationships of Cardiac Output, Blood Pressure, and Peripheral Resistance During Normal Respiration in Normotensive and Hypertensive Individuals, ibid. **4**:278 (Aug.) 1951. Chesky, K.; Moser, M.; Taymor, R. C.; Master, A. M., and Pordy, L.: Clinical Evaluation of the Ballistocardiogram: II. Heart Disease-Hypertension, Angina Pectoris, and Myocardial Infarction, Am. Heart J. **42**:328 (Sept.) 1951.

108. Makinson, D. H.: Changes in the Ballistocardiogram After Exercise in Normal and Abnormal Subjects, Circulation **2**:186 (Aug.) 1950.

109. Roseman, M. D., and Wasserman, E.: The Incidence of Hypertension in Mitral Stenosis, New England J. Med. **245**:450 (Sept. 20) 1951. Tricot, R.; Kandan, S., and Nychoyannopoulos, J.: Rétrécissement mitral et hypertension artérielle, Semaine hôp. Paris **27**:1996 (June 22) 1951.

110. Tricot, R.; Lachapelle, P., and Sibille, A.: L'hypertension "asystolique," Arch. mal. cœur **44**:806 (Sept.) 1951.

111. Milliez, P., and Fritel, D.: Les facteurs étiologiques prédisposant aux complications hypertensives de la grossesse, Semaine hôp. Paris **27**:163 (Jan. 14) 1951. Nordenstrahl, G.: Obstetrical Considerations in Essential Hypertension, Nord. med. **45**:433 (March 21) 1951. Jones, W. S.: Essential Hypertension with Superimposed Pre-Eclampsia, Am. J. Obst. & Gynec. **62**:387 (Aug.) 1951.

responses to tetraethylammonium chloride.[112] Permanent hypertension may become established during pregnancy, and its appearance during pregnancy should never be ignored.[113] An experimental state resembling toxemia may be produced in rats made hypertensive with desoxycorticosterone acetate by giving them renin injections.[114] Veratrum has been advocated for the treatment of eclampsia and preeclampsia.[115]

## TREATMENT

The mass of clinical literature on hypertension is now devoted to various forms of treatment. This is encouraging, since it denotes that therapeutic efforts are meeting with some success. However, the great variety of methods used[116] indicates either that most of them are nonspecific or that the natural course of the disease is so variable as to give false impressions of their efficacy.

*Surgical Treatment.*—Sympathectomy: This continues to be the most frequently employed surgical therapy in hypertension, and it is still the only method which may claim statistical validity on the basis of 5 to 10 year follow-up.[117] Short-term results[118] may appear to be more favorable, but the hypertension may return between 5 and 10 years postoperatively. Relief of symptoms (particularly headache) and signs (particularly retinopathy) may be striking even when little lowering of resting blood pressure is achieved.[119] The best late general results appear corre-

112. Govan, A. D. T.; Mukherjee, C. L.; Hewitt, J., and Harper, W. F.: Humoral Origin of Hypertension in Toxaemia of Pregnancy, J. Obst. & Gynaec. Brit. Emp. **58**:216 (April) 1951.

113. McKelvey, J. L.: Arteriosclerotic Pregnancy Toxemia, Am. J. Obst. & Gynec. **60**:510 (Sept.) 1950.

114. Masson, G. M. C.; Corcoran, A. C., and Page, I. H.: Experimental Production of a Syndrome Resembling Toxemia of Pregnancy, J. Lab. & Clin. Med. **38**:213 (Aug.) 1951.

115. Assali, N. S.: Studies on Veratrum Viride: Standardization of Intravenous Technique and Its Clinical Application in the Treatment of Toxemia of Pregnancy, Am. J. Obst. & Gynec. **60**:387 (Aug.) 1950.

116. (*a*) Page, I. H.: Treatment of Essential and Malignant Hypertension, J. A. M. A. **147**:1311 (Dec.) 1951. (*b*) Etienne-Martin, P.: Essai de classification anatomo-clinique de l'hypertension artérielle permanente essentielle, Semaine hôp. Paris **27**:3601 (Dec. 6) 1951.

117. Etienne-Martin, P.[116b]; Étude statistique de 46 hypertendus opérés: (Surrénalosplanchnicectomie, opération de Peet, opération de Pende), Semaine hôp. Paris **27**:3615 (Dec. 6) 1951; Étude comparative des différentes statistiques d'hypertendus opérés aux différents stades de la maladie, ibid. **27**:3622 (Dec. 6) 1951. Smithwick, R. H.: Hypertensive Cardiovascular Disease: Effect of Thoracolumbar Splanchnicectomy on Mortality and Survival Rates, J. A. M. A. **147**:1611 (Dec. 22) 1951. Thorpe, J. J.; Welch, W. J., and Poindexter, C. A.: Bilateral Thoracolumbar Sympathectomy for Hypertension: Study of 500 Cases, Am. J. Med. **9**:500 (Oct.) 1950. White, P. D.; Dimond, E. G., and Williams, A.: Follow-Up Study of 100 Private Hypertensive Patients with Cardiovascular Complications, J. A. M. A. **143**:1311 (Aug. 12) 1950.

118. (*a*) Ramos, J., and others: Tratamento cirúrgico da hipertensão arterial, Rev. paulista med. **38**:183 (March) 1951. (*b*) Govaerts, J., and Regnier, M.: Résultats du traitement chirurgical de l'hypertension dite "essentielle," Acta cardiol. **5**:473, 1950. (*c*) Conley, J. E., and Raine, F.: Sympathectomy for Hypertension: Experience with 52 Patients Followed 1 to 3 Years Postoperatively, Arch. Surg. **61**:810 (Nov.) 1950. (*d*) Chris, S. M.: Sympathectomy for Hypertension, Brit. M. J. **1**:665 (March 31) 1951.

119. Chris,[118d] Wertheimer, P., and Lecuire, J.: La thérapeutique chirurgicale de l'hypertension artérielle d'après 108 observations, J. med. Lyon **31**:819 (Oct. 5) 1950. Westerborn, A.: Results of Operation (Splanchnicotomy) for Hypertension: A Follow-Up of 47 Cases, Acta med. scandinav., Supp. 246, p. 268, 1950.

lated with the best sustained hypotensive effects,[120] although this correlation may not hold early after operation.[121] Some observers feel that the postural as well as the resting hypotensive effects are important in the general improvement.[122] Evidences of severe organic vascular disease, particularly of marked renal impairment are indications that surgery should not be tried or at least that long-term favorable effects should not be expected.[123] X-ray therapy over the thoracic sympathetic ganglia and splanchnic nerves[124] or to the carotid sinus[125] has been reported to result in clinical improvement in some patients.

Surgery for Pheochromocytoma: The possibility of surgical cure of hypertension due to pheochromocytoma has increased interest in it out of proportion with its frequency. A number of additional case reports have been published, and considerable stress has been laid on the use of pharmacological tests for diagnosing these tumors.[126] It seems fair to say that no one pharmacologic test is infallible

120. Whitelaw, G. P., and Smithwick, R. H.: Effect of Extensive Sympathectomy upon Blood Pressure Responses and Levels, Angiology **2**:157 (June) 1951.

121. Hoobler, S. W.; Manning, J. T.; Paine, W. G.; McClellan, S. G.; Helcher, P. O.; Renfert, H., Jr.; Peet, M. M., and Kahn, E. A.: The Effects of Splanchnicectomy on the Blood Pressure in Hypertension: A Controlled Study, Circulation **4**:173 (Aug.) 1951.

122. Evans, J. A.: Place of Splanchnicectomy in Treatment of Hypertension, Canad. M. A. J. **64**:47 (Jan.) 1951.

123. Simeone, F. A., and Ramirez, O.: Some Physiologic Effects of Lumbodorsal Sympathectomy for Hypertension, Surgery **28**:282 (Aug.) 1950.

124. Wolf, B.: Strahlentherapeutische Beeinflussung der Hochdruckkrankheit, Strahlentherapie **84**:559, 1951.

125. Audier, and Almaric: Le traitement des vertiges des hypertendus par la radiothérapie du sinus carotidien, Arch. mal. cœur **44**:913 (Oct.) 1951.

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and that the diagnosis of pheochromocytoma, as of other diseases, is made on the basis of the total clinical information available.

Resection of Coarctation of the Aorta: This may cure hypertension,[127] even in persons of the "essential hypertensive" age group.[128] However, reductions in blood pressure after such resections are not necessarily related to changes in renal hemodynamics.[129] Indeed, from recent experimental work it is doubtful that the hypertension of coarctation is "renal."[130]

Removal of Diseased Kidney: Relief of hypertension by removing a unilaterally diseased kidney has already been mentioned.[116b]

Fistula Production: Surgical production of large arteriovenous fistulas for the relief of essential hypertension would appear to have little experimental[131] or rational basis, but has been tried.

Adrenalectomy: The availability of adrenal cortex hormones for clinical use has allowed revival of a trial of subtotal and total adrenalectomy (with or without sympathectomy) for relief of severe hypertension.[132] A similar approach has been an attempt to produce adrenal sclerosis by injecting into the gland a sclerosing

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Routine Tests in Patients with Hypertension, J. A. M. A. **146**:1383 (Aug. 11) 1951. Conley, J. E., and Junkerman, C. L.: Lack of Specificity of Piperoxan Hydrochloride Test for Adrenal Medullary Tumors, ibid. **147**:921 (Nov. 3) 1951. Place, V. A.: Piperoxan Hydrochloride (Benzodioxan) Test: Report of a False Positive Reaction, ibid. **146**:1227 (July 28) 1951. Mandl, F.: Operation eines Phäochromocytom, Wien. med. Wchnschr. **101**:232 (March 31) 1951. McCoy, G. E., and Bridgeman, M. L. C.: Use of Drugs in the Diagnosis and Treatment of Pheochromocytoma: Case Report, Pediatrics **6**:286 (Aug.) 1950. Engel, A., and von Euler, U. S.: Diagnostic Value of Increased Urinary Output or Noradrenaline and Adrenaline in Phæochromocytoma, Lancet **2**:387 (Sept. 23) 1950. Arst, D. B.; Lahey, W. J., and Kunkel, P.: Pheochromocytoma, Yale J. Biol. & Med. **24**:26 (Sept.) 1951. Evans, J. A.; Rubitsky, H. J.; Bartels, C. C., and Bartels, E. C.: Re-Evaluation of the Reliability of Pharmacologic and Cold Pressor Studies in Hypertension and Pheochromocytoma, Am. J. Med. **11**:448 (Oct.) 1951.

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solution at the time of sympathectomy.[133] While there is little doubt the arterial pressure can be lowered by the production of adrenal insufficiency, it is too early to decide whether the long-term results justify this rather heroic method.

*Drug Therapy.*—The great number of drugs advocated for the treatment of hypertension can be divided into two large groups: the blocking drugs and the peripheral vasodilators. Of the blocking drugs,[134] the ganglionic blockers (particularly the methonium compounds) have received the most attention. Caution,[135] skepticism,[136] and in some instances frank opposition [135f] have been expressed concerning the clinical use of these powerful agents. They can cause profound hypotension especially in the upright position, but if continued in certain cases of severe hypertension, they may relieve symptoms and signs of severe or even malignant hypertensive vascular disease.[137] Side-reactions may be severe, tolerance usually develops, and the dosage range is unpredictable. Their use orally is particularly difficult, since so little of the drug is absorbed. More time and basic pharmacologic and physiologic studies [138] are needed to evaluate the place of these agents in the armamentarium against hypertension.[139]

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The adrenergic blocking drugs are also capable of profoundly lowering the blood pressure of hypertensives.[148a] Dibenamine® (N,N′-dibenzyl-β-chloroethylamine) hydrochloride, which acts peripherally, may cause hypotension and improvement in vascular signs, but causes undesirable side-effects.[140] Of the centrally acting adrenergic blockers, 1-hydrazinophthalazine is the most interesting.[141] It is said to cause renal vasodilatation and to be effective as a hypotensive agent both in renal hypertensive dogs and in hypertensive man. Much additional new information on this preparation is appearing in the current literature not covered by this review and undoubtedly more will be heard of it. On acute administration it causes postural hypotension, tachycardia, and headache, but with chronic oral administration in gradually increasing doses these side-effects are diminished. It is particularly useful in combination with other hypotensive drugs.

The dihydrogenated alkaloids of ergot represent another class of central adrenergic drugs. They produce postural hypotension, but in contrast to 1-hydrazinophthalazine, cause bradycardia, not tachycardia. They have been used mostly as "Hydergine" or CCK, a mixture of three alkaloids, dihydroergocornine (DHO), dihydroergocrystine (DHC), and dihydroergokryptine (DHK).[142] They have a mild hypotensive effect, to which patients apparently become resistant in about a month, but their most consistent effect is in providing symptomatic improvement, particularly in persons with labile hypertension.[143] It is said that the dihydrogenated alkaloids decrease the elevated "basal" metabolic rate observed in some hypertensives.[144] Incidentally, it is interesting that protein-bound iodine studies have not confirmed hyperactivity of the thyroid as of importance in hypertension.[145] The ergot derivatives have been used with moderate success in combination with veratrum.[146]

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Veratrum, which is probably a neurogenic vasodilator, not a blocking drug, has received considerable attention recently. It is a potent hypotensive substance, but its chronic use for the treatment of essential hypertension leaves considerable to be desired because of its emetic side-effect.[147] Its acute parenteral administration, if carefully controlled, can produce hypotension without nausea and vomiting and may improve exercise tolerance.[148]

The use of a prolonged course (30 days) of interrupted sedation with amobarbital sodium (sodium amytal®), widely used for the sedation test in hypertension, is reported to result in symptomatic improvement in most of the patients treated.[149] However, since amobarbital sodium is reported to cause a decrease in cardiac output, not in peripheral resistance,[150] it is doubtful that it should be classified as a vasodilator.

Rauwolfia serpentina, a crude root used in India for many years, is a mild hypotensive and bradycrotic agent, which has a sedative effect that is symptomatically helpful for many patients with hypertension.[151] It is currently receiving attention in this country.

Procaine used in daily intravenous injections for several days has been claimed to lower the blood pressure of hypertensive patients.[152] The use of pyrogens for a period of weeks hardly seems justified in spite of temporary improvement in symptoms and signs.[153]

Thiocyanate continues to be used in hypertension despite its toxic potentialities, necessitating most careful blood level control.[154] There seems little question that it is effective as a moderate hypotensive agent, but whether its general use is justified

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154. Parsonnet, A. E.; Simon, F., and Bernstein, A.: Low Dosage Potassium Thiocyanate in Treatment of Hypertension, J. M. Soc. New Jersey **47**:504 (Nov.) 1950. Aas, K., and Thingstad, R.: Thiocyanate Therapy of Hypertension: Further Experiences, Acta med. scandinav. **139**:229, 1951.

seems highly questionable.[155] Its exact mode of action is not understood, though it may have something to do with salt metabolism or at least with adrenal cortex function.[156]

*Dietary Treatment.*—There is now general agreement that dietary restriction in the form of the "rice diet" is capable of producing a hypotensive response and that sodium deprivation is the factor responsible for this effect.[157] The monotony, and in some cases the questionable if not adverse physiologic effects of this diet, preclude its general acceptance for very long periods, in spite of the fact that individual patients may show dramatic initial improvement on it.[158] As a result, no five-year series of continually treated patients has been reported, or seems likely to be.

## SUMMARY AND CONCLUSIONS

Hypertension remains a serious and unsolved problem. Progress in the understanding of its etiology and pathogenesis continues to be painstaking and slow. The therapeutic trial of a wide variety of hypotensive measures recently has received considerable attention and enjoyed some degree of success. It is possible that these therapeutic attempts may be more important in throwing light on the nature of the disease than in supplying a definite cure.

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# Case Reports

## TREATMENT WITH LARGE DOSES OF PENICILLIN IN A CASE OF SEVERE BACTEREMIA DUE TO PROTEUS

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ONE OF THE current problems in the control of infection in general hospitals is the treatment of infections due to Proteus organisms. The relative resistance of these organisms to antibiotics makes it likely that they will continue to be the survivors in situations in which secondary infection is inevitable and in which prophylactic chemotherapy is employed. This case report is presented to illustrate some of the difficulties encountered in the treatment of infections due to Proteus and to emphasize the effectiveness of large doses of penicillin in certain cases.

### REPORT OF CASE

The patient was a 45-year-old chronic alcoholic who was admitted to the Milwaukee County General Hospital because of a persistent low-grade fever. For 10 days prior to admission he was treated at another hospital for delirium tremens and a left lower lobe pneumonia. Treatment had consisted of administration of 3,000,000 units of procaine penicillin, 2 gm. of aureomycin, sedatives, fluids given parenterally, and large doses of vitamins. Pertinent history on admission was that he was a chronic alcoholic, had had a duodenal ulcer 10 years before, and had had nocturia and frequency of urination for many years.

The pertinent physical findings were temperature 99.6 F.[1], pulse rate 84 a minute, respirations 20 a minute, and blood pressure 120/70. The patient was a tremulous, asthenic, poorly nourished man who appeared chronically ill. Examination of the chest revealed it to be normal. The heart was unremarkable except for an early diastolic murmur just to the left of the sternum in the third interspace. The abdomen contained no palpable masses or organs. There was no flank tenderness. The prostate gland was of normal size and consistency.

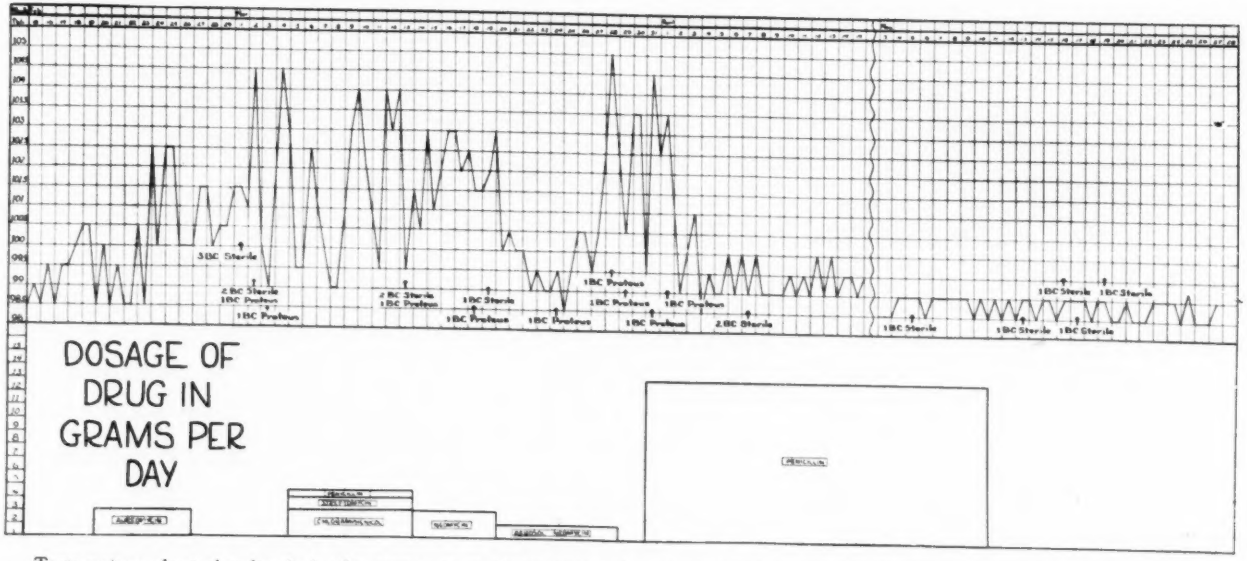
Pertinent laboratory data were as follows: hemoglobin 14 gm.; white blood cell count 9,100 per cubic millimeter, with 68% polymorphonuclear leucocytes; nonprotein nitrogen 29 mg. per 100 ml.; sedimentation rate 78 mm. per hour (Westergen); Wassermann test negative; agglutination test for Salmonella paratyphi, Brucella, and Proteus X-19 negative. A urinalysis revealed a specific gravity of 1.018, 1+ albumin, no sugar, and occasional white blood cells per high-power microscope field. The Mantoux skin test was negative. A roentgenogram of the chest revealed increased hilar markings in the middle third of the left lung which were thought to represent a resolving pneumonia.

The patient had a low-grade fever for the first five days in the hospital with no essential change in the clinical picture. Detailed data on the clinical course and on the antibiotics used are presented in the accompanying chart. Administration of aureomycin was started on an empirical basis, and 2.0 gm. daily was administered orally for one week. The temperature gradually began to rise and at the end of the course of aureomycin was spiking to 102 F. every day. A lumbar puncture done at this time revealed the spinal fluid to be normal. On the 16th hospital day three blood cultures were sterile. On the 17th hospital day the patient had a hard shaking chill and his temperature rose to 104 F. His blood pressure fell to 95/75. The urine output remained above 1,200 cu. ml. a day. One of three specimens of blood drawn on the 17th hospital day grew Proteus bacteria on culture. On the 18th hospital day the physical findings were essentially unchanged, but Proteus again was grown from the blood.

This study was aided by a grant from Parke, Davis & Company.

From the Medical Service of the Milwaukee County General Hospital and the Department of Medicine of the Marquette University Medical School.

1. All temperatures recorded in this report are oral.




Temperature chart showing lack of response to moderate doses of aureomycin, streptomycin, chloramphenicol, penicillin, and neomycin and clinical bacteriological cure when 12 gm. a day of penicillin was administered. The abbreviation *BC* represents "blood culture."

The clinical impression at that time was that the patient was showing the shock-like picture of Proteus bacteremia.[2] It was felt that the source of the infection was either an endocarditis, the infected area in the left lung, or the genitourinary system. Therapy was started with a combination of 2 gm. a day of chloramphenicol given orally, 1 gm. a day of streptomycin given intramuscularly, and 600,000 units of penicillin given intramuscularly. Bactericidal sensitivity tests by the tube dilution method [3] showed the strains of Proteus to be killed by the combination of 3.6 γ per milliliter each of chloramphenicol, streptomycin, and penicillin. Bacteriostatic sensitivity tests by the same method showed the organisms to be inhibited by smaller concentrations of streptomycin, penicillin, and neomycin than of aureomycin, chloramphenicol, or oxytetracycline ("terramycin") (Table 1). The combination of penicillin and chloramphenicol revealed the bacteriostatic potentiation and bactericidal inhibition that has been reported with other strains of Proteus (Table 2).[4] There was no apparent favorable response to combined therapy with chloramphenicol, streptomycin, and penicillin. After a nine-day course of this combined therapy the hemoglobin had fallen to 10 gm. and the white blood cell count was 7,000 per cubic millimeter, with 90% polymorphonuclear leucocytes. At this time Proteus was again cultured from the blood.

TABLE 1.—*The Sensitivity to Antibiotics of Four Cultures of Proteus Organisms Isolated from the Blood of the Patient**

| Inhibitory Concentration of Drug, γ per Ml. | Aureo | Chloro | Terra | Strepto | Pen | Neo |
|---|---|---|---|---|---|---|
| 3 | .. | .. | .. | 4 | .. | 4 |
| 6 | .. | .. | .. | .. | 2, 4 | 1 |
| 12 | .. | .. | .. | 1, 2 | 1, 3 | 2, 3 |
| 25 | 4 | .. | .. | 3 | .. | .. |
| 50 | 1, 2, 3 | 1, 4 | 4 | .. | .. | .. |
| 100 | .. | 2, 3 | 1, 2, 3 | .. | .. | .. |

* Aureo indicates aureomycin; Chloro, chloramphenicol; Terra, oxytetracycline ("terramycin"); Strepto, streptomycin; Pen, penicillin, and Neo, neomycin.
The cultures are numbered from 1 to 4.

TABLE 2.—*The Bacteriostatic Potentiation and Bactericidal Inhibition That Result When Chloramphenicol and Penicillin Are Combined Against Proteus**

| Inhibitory Concentration of Drug, γ per Ml. | Penicillin | Chloramphenicol | Penicillin and Chloramphenicol |
|---|---|---|---|
| 3 | .. | .. | X |
| 6 | .. | .. | .. |
| 12 | X O | .. | .. |
| 25 | .. | .. | O |
| 50 | .. | X | .. |
| 100 | .. | O | .. |

* X indicates bacteriostatic end-point, and O, bactericidal end-point.[3]

Two grams of neomycin daily was then administered intramuscularly for eight days. No effect on the course of the illness was noted, and a specimen of blood drawn on the fifth day of neomycin therapy again grew Proteus. Because a roentgenogram of the chest at this time revealed the persistence of the area of increased density at the base of the left lung, neomycin was administered by aerosol; 0.5 gm. dissolved in 2 ml. of 0.9% saline was administered twice a day for nine days. There was an apparent clinical response, with the temperature returning to normal for the first time in three weeks. However, three specimens of blood drawn while neomycin was being given by this method grew Proteus. At the end of nine days the temperature rose to 105 F. The patient appeared moribund, his blood pressure dropped to 85/65, and his respiratory rate was 25 a minute. All chemotherapy was discontinued for two days.

The case was reviewed and it was noted that the Proteus isolated from the blood was almost as sensitive to penicillin as it was to any of the other antibiotics (Table 1). Since penicillin

2. Waisbren, B. A.: Bacteremia Due to Gram-Negative Bacilli Other Than the Salmonella, A. M. A. Arch. Int. Med. **88**:467-488 (Oct.) 1951.

3. Waisbren, B. A.; Carr, C., and Dunnette, J.: The Tube Dilution Method of Determining Bacterial Sensitivity to Antibiotics, Am. J. Clin. Path. **21**:884-891 (Sept.) 1951.

4. Waisbren, B. A., and Carr, C.: Penicillin and Chloramphenicol in the Treatment of Infections Due to Proteus Organisms, Am. J. M. Sc. **223**:418-421 (April) 1952.

is the safest and the best-tolerated of the antibiotics, it was decided to administer 6 gm. of penicillin (10,000,000 units) dissolved in 250 ml. of 5% dextrose in water, intravenously, twice daily. Blood for culture drawn 24 hours after the administration of the penicillin again grew Proteus. However, within 48 hours after initiation of this therapy the patient appeared to be much improved. The temperature dropped to 99 F., the pulse rate dropped from 120 a minute to 72 a minute, and the blood pressure rose to 110/80. After three days of therapy with penicillin the patient became afebrile, and his temperature remained normal during the remainder of his hospital stay. The administration of penicillin was continued for 40 days. Seven specimens of blood drawn during this period were sterile. At the end of this time the patient was able to be up and around the ward. The diastolic murmur in the pulmonary region was no longer heard, and there was complete resolution of the area of density at the base of the left lung. An Addis count done a week before discharge revealed 1,920,000 red blood cells and 25,190,000 leucocytes. A urine culture grew Proteus. Four specimens of blood drawn after the administration of penicillin was discontinued were sterile.

The patient was followed in the outpatient department and was clinically well nine months after discharge from the hospital.

## COMMENT

Although streptomycin, neomycin, chloramphenicol, oxytetracycline ("terramycin"), and sulfisoxazole (gantrisin®) have been reported as being effective in Proteus infections, no one of these agents has been satisfactory in the majority of cases.[5] Helmholz and Sung [6] were the first to point out that penicillin was active against Proteus. More recently it was shown that some infections due to Proteus responded to penicillin used alone and in combination with chloramphenicol.[4]

When in vitro tests show equal sensitivity of Proteus to penicillin, streptomycin, neomycin, or oxytetracycline, penicillin may be the drug of choice because of the extremely high doses of this agent that can be administered with safety. On the other hand, in certain cases the infection can be cured only by combinations of antibiotics as determined by the tube dilution method.[2]

The in vitro sensitivity tests, done with the organisms isolated from this patient, confirmed previous work which showed that when penicillin and chloramphenicol are combined there is a decrease in bactericidal rate but a potentiation of bacteriostatic activity (Table 2).[7] Thus, whether or not these agents should be combined against infections due to Proteus may depend on whether a rapid bactericidal effect is needed or whether a sustained bacteriostatic action is desirable. In the first instance penicillin alone would be indicated and in the second the combination of penicillin and chloramphenicol might be used.

## SUMMARY

Clinical and laboratory studies on a patient suffering from severe Proteus bacteremia have been presented. This case serves to emphasize the effectiveness of penicillin in some infections due to Proteus organisms.

5. Waisbren, B. A., and Spink, W. W.: A Clinical Appraisal of Neomycin, Ann. Int. Med. **33**:1099-1110 (Nov.) 1950. Herrill, W. E.: Infections of Blood Stream and Heart, Symposium on Use of Chemotherapeutic and Antibiotic Agents, American Medical Association Annual Meeting, Chicago, June, 1952. Carrol, G.; Allen, N. N., and Flynn, H.: Gantrisin in an in Vivo and in Vitro Study of Urinary Infections, Urol. & Cutan. Rev. **53**:677-683 (Nov.) 1949. Waisbren.[2] Waisbren and Carr.[4]

6. Helmholz, H. F., and Sung, C.: Bactericidal Action of Penicillin on Bacteria Commonly Present in Infections of Urinary Tract, with Especial Reference to Streptococcus Faecalis, Am. J. Dis. Child. **68**:236-242 (Oct.) 1944.

7. Jawetz, E.; Gunnison, J. B., and Coleman, V. B.: The Combined Action of Penicillin with Streptomycin or Chloromycetin on Enterococci in Vitro, Science **111**:254-256 (March 10) 1950. Waisbren and Carr.[4]

# News and Comment

## ANNOUNCEMENTS

**American Occupational Therapy Association.**—The American Occupational Therapy Association will hold its Thirty-Sixth Annual Conference, Nov. 13 to 20, 1953, at the Shamrock Hotel, Houston, Texas.

**Change of Date of Annual Meeting of American Psychomatic Society.**—The American Psychomatic Society has changed the dates of its coming Annual Meeting. Instead of taking place in May, the meeting will be held on April 18 and 19, 1953, at Chalfonte-Haddon Hall, Atlantic City, N. J.

# Books

**The Esophagus and Its Diseases.** Eddy D. Palmer, M.D., F.A.C.P. Price, $15.00. Pp. 553, with illustrations. Paul B. Hoeber, Inc., 49 E. 33d St., New York 16, 1952.

Dr. E. D. Palmer, chief of the gastrointestinal section of Walter Reed Army Hospital, has provided an excellent textbook on diseases of the esophagus. This book begins with a summary of our present knowledge of the anatomy and physiology of the esophagus and goes on to an orderly discussion of all esophageal diseases whether they are common or uncommon. At the conclusion of each of the chapters there is an extensive series of references. This book is probably the most comprehensive text on diseases of the esophagus in the English language that is available at the present time.

Dr. Palmer has not included any chapters on the technic of esophagoscopy, nor is there any specific discussion of the roentgenology of the esophagus. The chapter on diaphragmatic hernias is relatively brief and is probably the least effective portion of the book. The details of surgical management of various esophageal diseases have received little attention. Specialists will find it necessary to consult the literature or textbooks on bronchoesophagology, thoracic surgery, or radiology. Nevertheless, Colonel Palmer has presented a well-rounded reference book on the esophagus which should be of great help to the general practitioner.

**Cellular Changes with Age.** By Warren Andrew, Ph.D., M.D. Price, $2.50. Pp. 74, with 25 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1952.

This little volume is a factual account of cellular changes occurring in various organs and tissues as the aging process develops. The illustrations are excellent. The conclusions are what one might expect, namely, that much more study is necessary before one can answer the question of why organisms grow old and die.

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*1. Humphreys, P., et al: Angiology 3:1 (Feb.) 1952. 2. Plotz, M.: New York State J. Med., 52:2012-2014 (Aug. 15) 1952. 3. Perlman, A.: Angiology 3:16 (Feb.) 1952. 4. Samuels, S.S., et al.: Angiology 3:30 (Feb.) 1952.*

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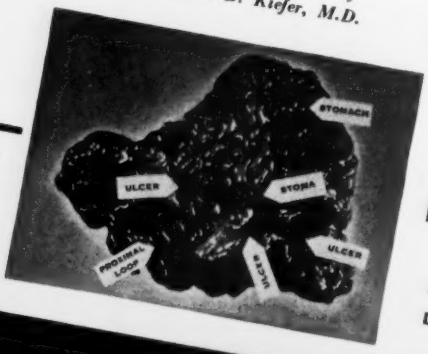


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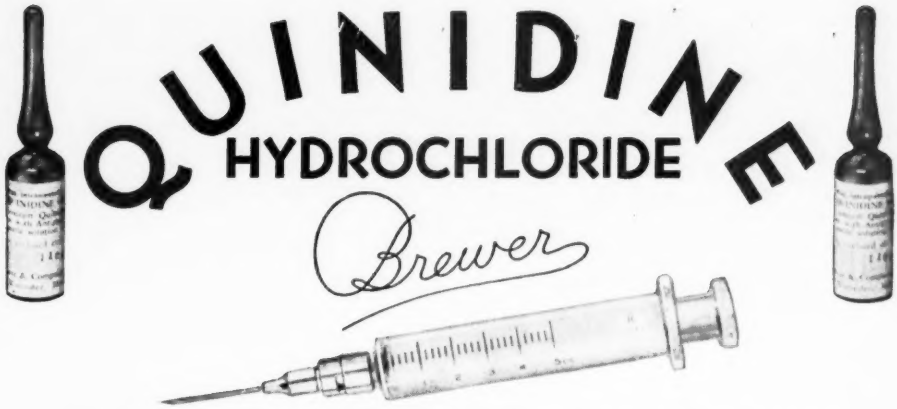


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3. Armbrust, Chas. A. Jr. and Levine, Samuel A.: Paroxysmal Ventricular Tachycardia: A Study of 107 Cases: Circulation, 1: 28-39 (Jan.) 1950
4. Bell, G. O.; Bradley, R. B.; and Hurxthal, L. M.: Paroxysmal Tachycardia, Experiences with Massive Doses of Quinidine Intravenously in a Refractory Case: Circulation, 1: 939 (April Part II) 1950


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